Pulmonology Journal

volume 26 / number 6 / November/December 2020

PULMONOLOGY JOURNAL

Previously **Revista Portuguesa de Pneumologia**

Editorials

Original articles

volume 26 / number 6 / November/December 2020

ISSN 2531-0437

www.journalpulmonology.org

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

36º CONGRESSO DE

PNEUMOLOGIA

2020 | **12-14** NOV | **EPIC SANA** ALGARVE

#SPP2020

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

www.sppneumologia.pt

Published every 2 months (6 issues per year).
www.journalpulmonology.org

Reprints information:
Clarissa Felix: c.felix@elsevier.com

Subscription of printed version available

One issue	30.00 € (VAT not included)
Anual	120.00 € (VAT not included)

(prices valid only for Portugal)

Subscriptions orders: sppneumologia@mail.telepac.pt

ELSEVIER
Av. Josep Tarradellas, 20-30, 1°
08029 Barcelona (Spain)
Phone: +34 932 000 711
Paseo de la Castellana, 163
28046 Madrid (Spain)
Phone: +34 914 021 212

Data protection: Elsevier España, S.L.U.. declares that it complies with that established by Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights (LOPDGDD).

Indexed in: Science Citation Index Expanded (SCIE), Journal of Citation Reports (JCR), Index Medicus/MEDLINE, Scopus, EMBASE/Excerpt Medica
ISSN 2531-0437 (online)

Register 122.190 of Gabinete para os Meios de Comunicação Social

Printed in Spain
Printed in acid free paper
Legal deposit: B-20.760-2019

PULMONOLOGY

PULMONOLOGY

www.journalpulmonology.org

Volume 26. Number 6. November-December 2020

CONTENTS

Letters to Editor

Correspondence

Book Commentary

Pulmonol. 2020;**26(6)**:333–334

PULMONOLOGY

www.journalpulmonology.org

EDITORIAL

The lung microbiome and pneumonia: Where precision medicine meets pulmonology

Human wellbeing is the result of dynamic networking between five nodes: mind–brain, genes, epigenetics, environment, and microbiome.[1] These nodes communicate with each other through messengers, including neuroendocrine peptides and microbial metabolites. One can imagine this grand system as a symphony orchestra except without a permanent conductor. To hear a well-tuned and performed symphony, a healthy state, the function of each node is synchronized with the other four. The disorder is the phenotype of any disturbance in the network.

So far, mostly our attention spectrum to study, prevent, and treat each disorder(s), has been narrowed to a limited cause and effect or association between an agent and the affected organ. When it comes to multisystem disorders like multiple system organ failures in a septic patient with pneumonia, our capability to prevent, predict and treat the patient is as good as the best survival rate for septic shock.

In this narrative review article, using the above-proposed model to study a disease, our new understanding of the pathogenesis of pneumonia and its potential implications for prevention, treatment, and policy-making are discussed.

The classic theory of the pathogenesis of pneumonia[2] assumes that the lung is a sterile organ, and the etiologic microorganism enters, colonizes, and invades pure airways and pulmonary parenchyma either through aspiration from the digestive tract or circulation. Advances in genetics techniques to detect microbes, like 16S rRNA gene sequencing[3] and metagenomics, have shown that the lung is not a sterile organ as we previously assumed. Indeed, a constellation of different microorganisms lives in small airways and alveoli. Compared with the gut microbiome, however, the density and diversity of the lung microbiome are limited. The lung was considered a sterile organ because the routine sputum cultures fail to detect anaerobic microorganisms.[4]

In healthy lungs, Proteobacteria, Firmicutes, and Bacteroidetes are the most commonly identified bacteria, while, Streptococcus, Prevotella, Fusobacteria, and Veillonella predominate, with potential pathogens, such as Haemophilus and Neisseria, are a smaller fraction of a healthy lung microbiome. Interestingly, the same bacterial population is the normal flora of the mouth in healthy individuals.[5] The formation and diversity of the pulmonary microbiome (PM) start with the exposure of newborn oral mucosa to maternal vaginal flora with subsequent microaspiration of the newly formed oral flora into the airways and alveolar epithelial cells. Microaspiration is the primary source of populating PM, inhalation and intestinal microbiome are other sources. Intestinal microbiome influences PM directly by the migration of microorganisms to PM via the lymphatic system, and indirectly, by immune modulation. Submucosal lymphocytes, dendritic cells, and macrophages exchange information with the intraluminal microbiome. These interactions set the immune tone and affect the function of immune cells in response to newly invading pathogens. Migrating immune cells from the intestine to bronchial submucosa and lung interstitial space by lymphatic flow, modulate the pulmonary defenses and susceptibility to virulent pathogens. Altered intestinal microbiome after broad-spectrum antibiotic therapy or intestinal ischemia in acute illness can increase the risk of developing pneumonia or ARDS.[6]

The content and diversity of the pulmonary microbiome at any given time depends on dynamic interactions between immigration, colonization, and elimination processes. Through aging, the diversity of the PM evolves and adapts to the living environment, diet, and submucosal immune tone, among other factors. For example, a high fiber diet by producing more short-chain fatty acids (SCFA) enhances Bacteroides dominance both in gut and lung. It has been shown that the high fiber diet can decrease the incidence of asthma.[6] Most studies of the PM focused on the bacterial population. However, it is expected that a variety of viruses and fungi are part of PM. All these microorganisms continuously communicate with each other and their host through their metabolites. Symbiosis is a dynamic, healthy state when PM has a ''normal'' diversity, and the host response/immune tone is well-tuned and adjusted. As a result of immigration and poor elimination of a hostile pathogen, altered immune tone, i.e., acute stress suppresses immunity, the PM diversity is reduced, and a

https://doi.org/10.1016/j.pulmoe.2020.04.005

dominant microorganism can act as a virulent pathogen, that provokes an inflammatory host response which is called the clinical phenotype of pneumonia. Bos et al. summarized this process as ''pneumonia could be defined in ecological terms as ''the acute loss of biodiversity due to the overgrowth of a single or several pathogenic microorganisms causing lung inflammation and damage.''[4]

It seems that PM diversity in a healthy state correlates with mouth microbiome diversity. It is well documented that the change in the oral microbiome is related to the severity of acute illness rather than the admission unit of the patient. This finding emphasizes the detrimental role of the patient's altered immune response to severe stress and its role in transforming symbiosis to dysbiosis.[7]

The practical question is how this new concept of developing pneumonia will change our diagnostic, therapeutic, and health administration policies of pneumonia. First, one cannot draw a sharp line between rigid definitions of ''community-acquired pneumonia'' vs. ''healthcare-associated pneumonia'' or ''ventilator-associated pneumonia.''

Increasingly, we encounter patients without a history of exposure to a health care environment that presents with Pseudomonas or Acinetobacter pneumonia. Based on the new concept, one can imagine that even a healthy person would have a few pathogenic gram-negative rods or gram-positive cocci in lower airways or alveolar epithelium. If PM diversity and immune tone maintain symbiosis, those pathogens will be contained and do not evoke a pathologic inflammatory response. In this view, even acute mental stress by changing the submucosal immune tone can promote dysbiosis and finally manifest as gram-negative rod (GRD) pneumonia.

This would account for the fact that, if a patient is being treated as ''community-acquired pneumonia'' with Ceftriaxone and Azithromycin, while the pathogen is an enteric GRD or methicillin-resistant staphylococcus aureus (MRSA), there would be a higher risk of treatment failure, morbidity, and mortality. To apply the personalized or precision medicine principles to patients with pneumonia, there are no other options than to optimize respiratory sampling and employ non-culture based microbiologic harvesting methods to detect the pathogenic microorganism(s) and tailor antibiotics against them. There is no doubt that shortly our guidelines will be changed to embrace the new concept and methodologies. Still, until then, for practitioners, the take-home message is by considering the new definition of pneumonia based on PM dynamics, we should be able to detect treatment failures faster and tailor antibiotics accordingly.

Applying the new concept to reimbursement policies by third-party payers as well as epidemiological studies, will uproot the current practices. For example, in the US, Medicare needs to revise its penalties based on narrow definitions of ventilator-associated pneumonia.

In conclusion: advancements in non-culture-based microorganisms detecting methods show that the lung has its dynamic microbiome that interacts with the host through symbiosis and causes pneumonia through dysbiosis. This concept will open the door for personalized/precision medicine in the diagnosis and treatment of pneumonia.

References

1. Thomas S, Izard J, Walsh E, Batich K, Chongsathidkiet P, Clarke G, et al. The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists. Cancer Res. 2017;77:1783–812.
2. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371:1619–28.
3. Watts G, Youens-Clark K, Slepian M, Wolk D, Oshiro M, Metzger G, et al. 16S rRNA gene sequencing on a benchtop sequencer: accuracy for identification of clinically important bacteria. J Appl Microbiol. 2017;123:1584–96.
4. Bos LDJ, Rylance J, Gordon SB. The lung bacterial microbiome in community-acquired and nosocomial pneumonia. In: Cox MJ, Ege MJ, von Mutius E, editors. The lung microbiome; ERS monograph. 2019. p. 188–94.
5. Dickson RP, Erb-Downward JR, Martinez FJ, Huffnagle GB. The microbiome and the respiratory tract. Annu Rev Physiol. 2016;78:481–504.
6. Marsland BJ, Trompette A, Gollwitzer ES. The Gut-Lung axis in respiratory disease. Ann Am Thorac Soc. 2015;12 Suppl. 2:S150–6.
7. Dickson RP. The microbiome and critical illness. Lancet Respir Med. 2016;4:59–72.

A. Araghi
Georgia College of Medicine, Augusta University, Augusta, GA, USA
Available online 29 May 2020

Pulmonol. 2020;**26(6)**:335–337

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Pulmonary telerehabilitation: An international call for action

The COVID-19 pandemic has impacted dramatically on people's lives and health care systems worldwide. Resources of the national health services have been focused on the monitoring and management of patients with COVID-19 and so chronic respiratory disease management, namely through pulmonary rehabilitation (PR), has become even more challenging than it used to be before COVID-19.

Following national and international recommendations, PR programmes were advised to suspend their activities and to provide care remotely using telehealth solutions (e.g., phone, video-calls, telerehabilitation).[1,2] Major concerns already existed about the lack of access to PR programmes (either hospital-, primary care- or community-based) worldwide.[3] In Portugal, the reported percentage of patients having access to PR programmes is between 0.5 and 2%.[4,5] This situation has most certainly been aggravated by the COVID-19 outbreak due to the interruption of PR, but also due to the increased number of patients with acquired respiratory diseases that is expected in the coming months. Given the high scientific evidence of PR in improving symptoms, physiological and psychosocial domains in patients with chronic respiratory disease, it is urgent to explore innovative avenues to overcome the past and present difficulties.[3]

During (and most certainly after) this outbreak, the implementation of different technological solutions allowed us to overcome many of the hindrances imposed by forced social distancing. This was the case of telerehabilitation strategies that in the short term have been largely focused on patients who had previous on-site access to PR and on patients with COVID-19.[6–10] In the long run, these may be feasible strategies to increase access to PR for those in need since patients eligible for PR have access to and feel confident using digital technologies.[11] But how prepared are health services to implement telerehabilitation?

According to the World Health Organization, telehealth is the ''delivery of health care services, where patients and providers are separated by distance through the use of information and communications technology (ICT).[12] Telehealth can be employed in several clinical areas, such as teleradiology, teledermatology, telepsychiatry and telerehabilitation. Telerehabilitation has been previously defined as the delivery of rehabilitation through a variety of ICT. Similarly to telehealth, this definition still encompasses a large diversity of procedures within the realm of rehabilitation, where PR can be included.[13] However, pulmonary telerehabilitation is far from being a reality yet. For example in Portugal, in the most recent characterisation of PR, from the 24 centres delivering PR programmes, none was telehealth supported.[4] Although efforts to increase access to PR have been made recently (primary care centres were advised to implement programmes in well-selected patients),[14] telerehabilitation guidance was never provided.

The use of telehealth is increasingly included in national health services.[12] In Portugal there has been a TeleHealth National Centre dedicated to the development and implementation of telehealth solutions since 2016.[15] This centre has produced guidance for teleconsultation, teleradiology, teledermatology and remote patient monitoring. Yet, guidelines for telerehabilitation are still missing. A similar scenario is present in several countries worldwide and therefore guidelines for telerehabilitation are urgently needed but should be broad enough to adapt to all types of rehabilitation.

A fundamental pillar of PR programmes is its multidisciplinary nature to address the needs of patients with chronic respiratory diseases and therefore, to standardise pulmonary telerehabilitation, a joint effort by national organisations, scientific and professional societies is required. This effort should also be developed in articulation with the most relevant international societies in the area of respiratory medicine, such as the European Respiratory Society (ERS) and the American Thoracic Society (ATS). Despite the recognised difficulties, e.g., ATS has publicly acknowledged not being able to endorse a specific approach to PR during the current challenges,[16] it is urgent to find alternatives to conventional PR, whilst seeking to increase access to a higher number of patients who can benefit.

In the process of developing guidelines for telerehabilitation, it could be of interest to start by analysing the available examples of PR programmes already being delivered remotely to patients with chronic respiratory diseases.[17–19] The available literature reports telerehabilitation to be as effective as onsite-PR programmes and with potential for successful implementation even with few resources in patients' homes.[20] Combining this previous knowledge with the experience gathered from the implementation of telerehabilitation in patients with COVID-19 is now required.[9,21,22]

https://doi.org/10.1016/j.pulmoe.2020.05.018

Pulmonary rehabilitation, even if delivered remotely must preserve its cornerstone components, i.e., exercise training, education, and behaviour change but, a serious debate about the selection criteria, outcome measures, emergency plans, intervention design and equipment/technology is needed. The discussion should also involve technological specialists to aid healthcare providers in selecting and combining cost-benefit and friendly-user telemonitoring technology such as respiratory monitors, pulse oximeters, activity trackers, environmental sensors, monitors of physiological variables (e.g., heart rate, blood pressure, temperature) and communication systems.[23] Concerns about sharing data and meeting General Data Protection Regulation (GDPR) requirements when using the different telemonitoring systems also need to be addressed. Additionally, a significant effort may be needed to try to preserve the social component of PR the role of which is indusputable during on-site programmes but may be lost during telerehabilitation.

Different discussions involving all relevant stakeholders in PR, from patients and families to healthcare providers, policy makers and scientists are urgently needed to shift PR from conventional to telerehabilitation and increase access to this fundamental intervention. Telerehabilitation can be a sustainable solution to the increasing burden of chronic respiratory diseases worldwide.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Direção-Geral da Saúde. Orientação n° 020/2020 de 03/04/2020: COVID-19: FASE DE MITIGAÇÃO Cuidados de Reabilitação e Respiratórios Domiciliários. URL: https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0202020-de-03042020-pdf.aspx [accessed 21.05.20].
2. National Health Service. Clinical guide for the management of respiratory patients during the coronavirus pandemic. URL: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0063-Specialty-guide-_Respiratory-and-Coronavirus-_v1_26-March.pdf [accessed 25.05.20].
3. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. Am J Respir Crit Care Med. 2015;192:1373–86.
4. Programa Nacional para as Doenças Respiratórias 2012-2016. Relatório de análise da capacidade instalada de reabilitação respiratória nos hospitais do serviço nacional de saúde; 2015. URL: https://www.dgs.pt/portal-da-estatistica-da-saude/diretorio-de-informacao/diretorio-de-informacao/por-serie-506885-pdf.aspx?v=%3d%3dDwAAAB%2bLCAAAAAAABAArySzItzVUy81MsTU1MDAFAHzFEfkPAAAA [accessed 21.05.20].
5. Observatório Nacional das Doenças Respiratórias. 13° Relatório do Observatório Nacional das Doenças Respiratórias; 2018. URL: https://www.ondr.pt/files/Relatorio_ONDR_2018.pdf [accessed 21.05.20].
6. Pan American Health Organization. Rehabilitation considerations during the COVID-19 outbreak. URL: https://iris.paho.org/bitstream/handle/10665.2/52035/NMHMHCOVID19200010_eng.pdf?sequence=6&isAllowed=y [accessed 25.05.20].
7. Balbi B, Berney S, Brooks D, Burtin C, Clini E, Franssen FME, et al. Report of an ad-Hoc International task force to develop an expert-based opinion on early and short-term rehabilitative interventions (after the acute hospital setting) in COVID-19 survivors (version April 3, 2020). URL: https://ers.app.box.com/s/npzkvigtl4w3pb0vbsth4y0fxe7ae9z9 [accessed 25.05.20].
8. Zhao H-M, Xie Y-X, Wang C. Recommendations for respiratory rehabilitation in adults with COVID-19. Chin Med J. 2020. PMID: 32251002.
9. Yang L-L, Yang T. Pulmonary rehabilitation for patients with coronavirus disease 2019 (COVID-19). Chron Dis Transl Med. 2020. PMID: 32411496.
10. Vitacca M, Carone M, Clini EM, Paneroni M, Lazzeri M, Lanza A, et al. Joint statement on the role of respiratory rehabilitation in the COVID-19 crisis: the Italian position paper. Respiration. 2020.
11. Jácome C, Marques F, Paixao C, Rebelo P, Oliveira A, Cruz J, et al. Embracing digital technology in chronic respiratory care: surveying patients access and confidence. Pulmonology. 2020;26:56–9.
12. World Health Organization. Telehealth: analysis of third global survey on eHealth based on the reported data by countries; 2016. URL: https://www.who.int/gho/goe/telehealth/en/ [accessed 21.05.20].
13. Hoaas H, Andreassen HK, Lien LA, Hjalmarsen A, Zanaboni P. Adherence and factors affecting satisfaction in long-term telerehabilitation for patients with chronic obstructive pulmonary disease: a mixed methods study. BMC Med Inform Decis Mak. 2016;16:26.
14. Direção-Geral da Saúde. Orientação Clínica 014/2019 Programas de Reabilitação Respiratória nos Cuidados de Saúde Primários. URL: https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0142019-de-070820191.aspx [accessed 21.05.20].
15. Centro Nacional de TeleSaúde. Plano estratégico nacional para a telessaúde 2019-2022. URL: http://www.cnts.min-saude.pt/wp-content/uploads/2019/12/PENTS_PT.pdf [accessed 21.05.20].
16. Garvey C, Holland A, Corn J. Pulmonary rehabilitation resources in a complex and rapidly changing world. URL: https://www.thoracic.org/members/assemblies/assemblies/pr/resources/pr-resources-in-a-complex-and-rapidly-changing-world-3-27-2020.pdf [accessed 21.05.20].
17. Santos CD, Neves RCd, Rodrigues F, Bárbara C. PC 190. First steps on home-based pulmonary telerehabilitation by Centro Hospitalar Universitário Lisboa Norte. Pulmonology. 2019;25(SC3):120–1.
18. Hansen H, Bieler T, Beyer N, Kallemose T, Wilcke JT, Østergaard LM, et al. Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. Thorax. 2020;75:413–21.
19. Selzler AM, Wald J, Sedeno M, Jourdain T, Janaudis-Ferreira T, Goldstein R, et al. Telehealth pulmonary rehabilitation: a review of the literature and an example of a nationwide initiative to improve the accessibility of pulmonary rehabilitation. Chron Respir Dis. 2018;15:41–7.
20. Vasilopoulou M, Papaioannou AI, Kaltsakas G, Louvaris Z, Chynkiamis N, Spetsioti S, et al. Home-based maintenance telerehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. Eur Respir J. 2017;49, 1602129.
21. Mukaino M, Tatemoto T, Kumazawa N, Tanabe S, Katoh M, Saitoh E, et al. Staying active in isolation: telerehabilitation for individuals with the severe acute respiratory syndrome coronavirus 2 infection. Am J Phys Med Rehabil. 2020;99:478–9.
22. Exum E, Hull BL, Lee ACW, Gumieny A, Villarreal C, Longnecker D. Applying telehealth technologies and strategies to provide acute care consultation and treatment of patients

with confirmed or possible COVID-19. J Acute Care Phys Therapy. 2020, http://dx.doi.org/10.1097/JAT.0000000000000143, publish ahead of print.
23. Angelucci A, Aliverti A. Telemonitoring systems for respiratory patients: technological aspects. Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2019.11.006, publish ahead of print.

C. Jácome[a,b,*], A. Marques[c,d], A. Oliveira[c,e,f], L.V. Rodrigues[g,h], I. Sanches[i]

[a] *Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University of Porto (FMUP), Porto, Portugal*
[b] *Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), University of Porto Faculty of Medicine, Porto, Portugal*
[c] *Lab3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences, University of Aveiro (ESSUA), Aveiro, Portugal*
[d] *iBiMED – Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal*
[e] *School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada*
[f] *West Park Healthcare Centre, Toronto, ON, Canada*
[g] *Pulmonology Department, Unidade Local de Saúde da Guarda E.P.E. – Hospital Sousa Martins, Portugal*
[h] *Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal*
[i] *Pulmonology Department, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal*

[*] Corresponding author.
E-mail address: cjacome@med.up.pt (C. Jácome).
Available online 24 June 2020

Pulmonol. 2020;**26(6)**:338–339

PULMONOLOGY

www.journalpulmonology.org

EDITORIAL

Will the COVID tsunami be able to impose tele-rehabilitation as a system opportunity?

We accept with enthusiasm the call by Jacome et al. published in this issue of Pulmonology.[1] Pulmonary rehabilitation may be used for a wide range of purposes and may include decreasing hospital care services, reducing the cost of care, improving adherence to physical activities, training and correcting life styles, improving accessibility, extending services to remote locations, improving self-monitoring, better understanding of prescribed treatments, improving adherence and better communication with health professionals.[2]

Tele-health has been defined as the use of information and communication technologies to deliver health care services and transmit medical data over long and short distances.[3] It encompasses a wide variety of technologies such as videoconferencing, internet platforms, store-and-forward devices, streaming media, and ground and wireless communication. Tele-rehabilitation works to address a basic question: how to improve access to rehabilitation services for patients, in an efficacious, cost-effective, and safe manner? It may provide an ideal opportunity to either improve access to pulmonary rehabilitation (PR) and/or help maintain positive results following a traditional program. Tele-rehabilitation reduces barriers such as insufficient programs and inadequate numbers of qualified health professionals, particularly in rural and regional areas, reduces problems of transportation, accessible parking, as well as walking distance from parking to the hospital. An emerging area of application of technology refers to the use of wearable sensors to facilitate the implementation of home-based rehabilitation interventions. Systems that aim to facilitate the implementation of rehabilitation exercise programs often leverage the combination of sensing technology and interactive gaming or virtual reality (VR) environments.[4]

Previous studies illustrated the potential of tele-health to facilitate the delivery of PR to patients with chronic obstructive pulmonary disease in their home, as well as to remote settings without the benefits of an established program.[5,6] The Coronavirus (COVID-19) pandemic ''day after'' is coming and people, who suffered from mild to severe pneumonia up to hypoxemic respiratory failure, might be at risk of long-term impairment and disability.[7]

Like all patients who have undergone critical illnesses, COVID-19 patients can present dyspnoea and fatigue at rest and during activities of daily living, disability, exercise intolerance, reduction in peripheral muscle function and in nutritional status with significant weight loss. In particular, they may be at risk of residual or worsening parenchymal damage with respiratory muscle function impairment. Furthermore, the infection can negatively affect also other organs like heart, kidneys, muscles and brain, with significant health impacts that may persist. Additionally, people requiring intensive care are at increased risk of post-traumatic stress disorder, anxiety, and depression.[8,9]

The newly discovered Coronavirus (COVID-19) and the rigorous request for social distancing has put tele-health (tele-coaching/tele-monitoring/telerehabilitation) in the front line. Tele-rehabilitation may represent the most appropriate response in the post-acute COVID phase by combining need for rehabilitation with need for social distancing.[10] It should be adopted in post COVID patients with mild to moderate disabilities, who need frequent monitoring, reside in isolated areas or are not available to participate in standard programs. Our recent experience in this field in a subgroup of post COVID patients (unpublished data) with reduced exercise tolerance, exercise induced desaturation, mild restrictive ventilatory pattern and persistent pathological lung imaging, has given promising results: average adherence to a 30-day program was 88% with improvement in exercise tolerance, dyspnoea and muscle fatigue. Strong monitoring should be maintained through wireless devices and when available wearable technology. Contacts by video-call or phone in order to verify patient adherence to rehabilitation sessions and quality of signals are needed. Despite this preliminary observation, the ideal post COVID candidate, duration of intervention, demonstration of efficacy equivalent to a traditional rehabilitation program to be applied and cost effectiveness are still unknown. Many patients who attend rehabilitation programs are older and may not be using, or have

https://doi.org/10.1016/j.pulmoe.2020.08.005

the capacity to use the technology required to delivery tele-rehabilitation. These factors may influence the tele-rehabilitation care environment, and as a consequence, the health outcomes. Patient empowerment and digital health literacy are essential for successful e-Health deployment. Another uncertainty in post COVID patients is the aim that is expected: a substitute for standard programs? purely reinforcement? maintenance program? a modality to improve access? Lack of different modalities of supervision is a crucial point: how to evaluate frequency, intensity, types and timing and how to monitor patients' adherence remain an unsolved question. Also the time required from staff as well as the amount of data to be interpreted in real time need to be elucidated. Proper training of health professionals and checking the technological requirements, especially in the patient's home, are also required. Adequate caregiver support may be necessary in cases of residual disability or for technological setting up. Legal problems associated with tele-rehabilitation are still controversial. The patient must be fully aware of the characteristics of the service, the potential risks, the precautions to reduce them and to ensure the confidentiality of the information.[11] The associated safety issues are complex and include not only apprehension about malfunctioning equipment, but also concerns regarding potential adverse effects on patient management decisions through delayed or missing information, misunderstood advice, or inaccurate findings.[12] Last but not least, the type of equipment used could represent a different per-patient cost, while currently there is insufficient evidence to properly advise about cost-effectiveness. How to perform quality control and modality of reimbursement remains a challenge.

The use of tele-health technology promises to address some major barriers for pulmonary rehabilitation delivery in that it allows for distribution of healthcare services and exchange of information between a healthcare provider and a patient in different geographical locations and therefore can provide an important resource to reach people who live in remote communities or have difficulty accessing traditional centres. National governments should promote common, ethical, legal, regulatory, technical, administrative standards for remote rehabilitation providing safe and effective services. The potential of Tele-rehabilitation has the enticing potential of reducing barriers and improving care. However, much of the research to date has not explored the impact of its introduction at a systems level, incorporating data beyond efficacy in the planning and implementation.

In conclusion we join the international call,[1] looking towards wider participation and operative actions.

Funding

This work was supported by the ''Ricerca Corrente'' funding scheme of the Italian Ministry of Health.

Conflict of interest

The author does not report any conflict of interest.

References

1. Jácome C, Marques A, Oliveira A, Rodrigues LV, Sanches I. Pulmonary telerehabilitation: an international call for action. Pulmonology. 2020;26, http://dx.doi.org/10.1016/j.pulmoe.2020.05.018. S2531-0437(20)30135-5.
2. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188:e13–64.
3. Standardization IOf. ISO Strategy for Services - Case study 1: International SOS (ISO/TS 13131, Telehealth services); 2016.
4. Angelucci A, Aliverti A. Telemonitoring systems for respiratory patients: technological aspects. Pulmonology. 2020;26:221–32, http://dx.doi.org/10.1016/j.pulmoe.2019.11.006.
5. Vasilopoulou M, Papaioannou AI, Kaltsakas G, Louvaris Z, Chynkiamis N, Spetsioti S, et al. Home-based maintenance telerehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. Eur Respir J. 2017;49:1602129.
6. Holland AE, Mahal A, Hill CJ, Lee AI, Burge AT, Cox NS, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. Thorax. 2017;72:57–65, http://dx.doi.org/10.1136/thoraxjnl-2016-208514.
7. Vitacca M, Carone M, Clini EM, Paneroni M, Lazzeri M, Lanza A, et al. Joint statement on the role of respiratory rehabilitation in the COVID-19 crisis: the Italian position paper. Respiration. 2020;99(6):493–9, http://dx.doi.org/10.1159/000508399.
8. Marchioni A, Tonelli R, Sdanganelli A, Gozzi F, Musarò L, Fantini R, et al. Prevalence and development of chronic critical illness in acute patients admitted to a respiratory intensive care setting. Pulmonology. 2020;26:151–8, http://dx.doi.org/10.1016/j.pulmoe.2019.09.006.
9. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Casa GD, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020;8(8):750–2.
10. Vitacca M, Lazzeri M, Guffanti E, Frigerio P, D'Abrosca F, Gianola S, et al. An Italian consensus on pulmonary rehabilitation in COVID-19 patients recovering from acute respiratory failure: results of a Delphi process. Monaldi Arch Chest Dis. 2020;(June):90, http://dx.doi.org/10.4081/monaldi.2020.1444.
11. Vitacca M, Paneroni M, Ambrosino N. Pulmonary rehabilitation in post acute patients with Covid-19. In: Donner CF, Ambrosino N, Goldstein RS, editors. Pulmonary Rehabilitation. 2nd edition CRC Press Pub.; 2020. p. 503–10.
12. Bauer KA. The ethical and social dimensions of home-based telemedicine. Crit Rev Biomed Eng. 2000;28:541–4.

Michele Vitacca*
Istituti Clinici Scientifici Maugeri IRCCS, Respiratory Rehabilitation of the Institute of Lumezzane, Brescia, Italy

* Correspondence to: Istituti Clinici Scientifici Maugeri IRCCS, Via S. Maugeri 4, 27100 Pavia, Italy.
E-mail address: michele.vitacca@icsmaugeri.it

19 August 2020
Available online 6 September 2020

Pulmonol. 2020;**26(6)**:340–345

PULMONOLOGY

www.journalpulmonology.org

COMMENT

The scientific production during 2009 swine flu pandemic and 2019/2020 COVID-19 pandemic

T.A. Carvalho[a,b,1], T.M. Lima[a,b,1], V.F. Melani[a,b,1], M.F. Mendes[a,b,1], L.R. Pereira[a,b,1], F.A.L. Marson[a,b,*,1]

[a] *Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds, São Francisco University, Bragança Paulista, São Paulo, Brazil*
[b] *Laboratory of Human and Medical Genetics, São Francisco University, Bragança Paulista, São Paulo, Brazil*

Received 29 May 2020; accepted 12 July 2020

KEYWORDS
COVID-19;
Lung disease;
H1N1;
Pandemic;
SARS-CoV-2;
Virus

The 2009 swine flu pandemic caused by Influenza A virus subtype H1N1 (H1N1) virus affected more than 214 countries and overseas territories or communities and over 18,449 deaths caused by the H1N1 infection[1] were confirmed. After ten years, a new pandemic named Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus emerged in 2019 in the city of Wuhan, China. Both diseases were declared a pandemic by the World Health Organization (WHO), swine flu on 24th April 2009 and COVID-19 on 11th March 2020. To date, 7th July 2020, the COVID-19 disease affected nearly 12 million inhabitants reaching 213 countries and territories around the world and two international conveyances. In addition, ∼550,000 deaths were associated with the disease in 185 locations worldwide. The COVID-19 started in China and spread worldwide changing its epicenter first to Europe, followed by the United State of America and, now, from May to July 2020 South America, mainly affecting patients in Brazil causing the health system to collapse in several states such as Amazonas and Rio de Janeiro. On 7th July

* Corresponding author at: University of São Francisco, Post graduate Program in Health Science, Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds and Laboratory of Human and Medical Genetics, Avenida São Francisco de Assis, 218, Jardim São José, Bragança Paulista, São Paulo 12916-900, Brazil.
E-mail addresses: tati.aline@hotmail.com (T.A. Carvalho), tainamomessolima65@gmail.com (T.M. Lima), vivismelani@gmail.com (V.F. Melani), matheus.ferreira@mail.usf.edu.br (M.F. Mendes), leticiarogini@gmail.com (L.R. Pereira), fernandolimamarson@hotmail.com, fernando.marson@usf.edu.br (F.A.L. Marson).
[1] The authors contributed equally to this study.

https://doi.org/10.1016/j.pulmoe.2020.07.009

2020, Brazil presented a total number of 1,674,655 patients with COVID-19; 535,558 active cases and 1,072,229 clinically recovered cases, 66,868 deaths related to the disease, and a case fatality rate of 3.99. Brazil occupies the 105 position worldwide for the number of real-time polymerase chain reaction by one million of inhabitants to screen SARS-CoV-2 virus.[2,3]

Both the 2009 swine flu pandemic and 2019/2020 COVID-19 pandemic resulted in a high number of published articles in a short period of time. The number of publications can be associated with the great impact on science in several areas including medicine, sociology, environment, physics, mathematics, biology and many other knowledge areas that act individually or are multidisciplinary in scope. Another striking aspect is that the collection of articles and other resources on the COVID-19 outbreak, including clinical reports, management guidelines, and comments are freely available to be used by researchers, health professionals and the community. The free availability of data resulted from the commitment of top scientific (e.g. *Science and Nature*) and Medical (e.g. *New England Journal of Medicine and Lancet*) journals to supply online articles fast and free of charge. To date, the Public Health Emergency COVID-19 Initiative has over fifty authors publishing (collaborators) that have volunteered to make their coronavirus-related articles accessible in PubMed Central® in formats and under license terms that facilitate text mining and secondary analysis.

In our study, a comparison was made between both pandemics regarding the number of publications divided into six main themes as follows: (i) the number of articles related with each disease caused by H1N1 virus and SARS-CoV-2 virus; (ii) the number of articles related with each disease considering the theme diagnosis; (iii) the number of articles related with each disease considering the theme symptoms; (iv) the number of articles related with each disease considering the theme epidemiology; (v) the number of articles related with each disease considering the theme treatment; and (vi) the number of articles related with each disease considering the theme vaccine. Each theme was individually analyzed and no exclusion was carried out using a specific theme as dominant because each theme cooperated equally to improve the Scientific knowledge during both pandemics. Moreover, one article can contain information about two (or more) themes with equal contextualization.

The data search was done using the PubMed (Public/Publisher MEDLINE) (https://pubmed.ncbi.nlm.nih.gov) using of the following descriptors: (i) (swine flu OR H1N1 OR H1N1 influenza virus OR influenza virus OR H1N1 influenza OR H1N1/09 OR H1N1 virus OR A(H1N1)pdm09 OR H1N1 flu OR Mexican flu OR influenza A); (ii) (coronavirus disease-19 OR coronavirus disease OR corona virus OR COVID-19 OR COVID19 OR SARS-CoV-2); (iii) the descriptors of (i) and (ii) were used along with the following descriptors: (iiia) AND (diagnosis); (iiib) AND (symptoms); (iiic) AND (epidemiology); (iiid) AND (treatment); (iiie) AND (vaccine). The data extraction was carried out weekly for ten weeks after the WHO declared the swine flu (25th April 2009) and COVID-19 (11th March 2020) as pandemic (Table 1 shows the periods of analysis).

The proportion between the number of published articles for COVID-19 and H1N1 pandemics was also set in our data. Only published studies written in English (filter 1) and about Human species (filter 2) were evaluated. In addition, in the PubMed, the advanced search tool was used to limit the time to collect the number of studies as previously described and the terms ''Date - completion'' were considered to give only the information about the studies published as their final version. In brief, the number of articles published for both pandemics and the proportion between them are shown in Table 1.

To improve the information about the studies published during both pandemic periods, the number of articles collected throughout the ten weeks after the WHO declared the swine flu and COVID-19 diseases as pandemic were categorized using the description for article type from PubMed as follows: case report, comment, letter to the editor, editorial, journal article, comparative study, observational study, clinical study, clinical trial (phase I, phase II, phase III or phase IV), randomized controlled trial, controlled clinical trial, guidelines, review, systematic review, meta-analysis, retracted publication or retraction of publication (Table 2). The percentage of each type of study was calculated based on the total number of articles published during each follow-up period.

The number of published articles about each virus or pandemic showed different numbers of publications during the first weeks after the WHO declared the two diseases a pandemic. The difference for the number of articles between pandemics improved because the number of studies about COVID-19 presented a faster increase, achieving four-times the number of publications about the swine flu pandemic from week 7 to week 10 after the WHO declared the swine flu and COVID-19 as pandemic. The same result was found when the studies were grouped for diagnosis, symptoms, epidemiology and treatment. However, the ''vaccine'' term was associated with a lower number of publications for COVID-19 pandemic when compared with the swine flu pandemic, showing only $\sim$0.48 of the number of studies during the first two weeks after the WHO declared the diseases as pandemics. However, the number of publications for COVID-19 pandemic achieved the mark of $\sim$0.77 when compared to swine flu pandemic during the week 10.

Science is crucial to promoting knowledge based on evidence and appears as a central pillar during critical events such as the two pandemics described in our data. The time lapse between the two events (pandemics) was only ten years and differences occurred in the number of publications considering the topics concerned. The higher number of studies published during the second evaluated period, namely COVID-19 pandemic, is evident. However, also noticeable is the higher number of case reports (N = 190), comments (N = 357), editorials (N = 495) and letters to the editors (N = 585) during the COVID-19 pandemic which increased the number of studies during this pandemic. These types of papers represent the lowest levels of the evidence pyramid showing a higher risk of bias,[5] also, these types of studies promote the possibility of fast discussion and dialogue among specialists, favoring better insights for future investigations. Moreover, the number of studies including the need for individual protection equipment and social isolation to control the dissemination of the SARS-CoV-2 virus is evident in the literature, highlighting the need of psychological care.[5–8] Likewise, the number of reviews, systematic reviews and meta-analysis including information

Table 1 Number of publications after the World Health Organization (WHO) declared swine flu disease (2009) and COVID-19 (2020) disease as pandemics distributed in a period of ten weeks.

Virus	Period	Week since pandemic by WHO	Virus/pandemic	Diagnosis	Symptoms	Epidemiology	Treatment	Vaccine
H1N1	2009/04/25–2009/04/25	1 (Fist day)	0	0	0	0	0	0
COVID-19	2020/03/11–2020/03/11	1 (Fist day)	0	0	0	0	0	0
H1N1	2009/04/25–2009/05/02	Week 1	41	13	14	19	21	15
COVID-19	2020/03/11–2020/03/18	Week 1	177	60	62	108	82	16
		Proportion	4.32	4.62	4.43	5.68	3.90	1.07
H1N1	2009/04/25–2009/05/09	Week 2	104	21	23	42	61	56
COVID-19	2020/03/11–2020/03/25	Week 2	331	123	131	213	168	27
		Proportion	3.18	5.86	5.70	5.07	2.75	0.48
H1N1	2009/04/25–2009/05/16	Week 3	150	36	36	58	88	80
COVID-19	2020/03/11–2020/04/01	Week 3	402	148	158	252	216	34
		Proportion	2.68	4.11	4.39	4.34	2.45	0.43
H1N1	2009/04/25–2009/05/23	Week 4	200	57	57	78	119	107
COVID-19	2020/03/11–2020/04/08	Week 4	598	219	229	356	322	52
		Proportion	2.99	3.84	4.02	4.56	2.71	0.49
H1N1	2009/04/25–2009/05/30	Week 5	245	67	67	101	146	125
COVID-19	2020/03/11– 020/04/15	Week 5	863	300	320	510	473	74
		Proportion	3.52	4.48	4.78	5.05	3.24	0.59

Table 1 (*Continued*)

Virus	Period	Week since pandemic by WHO	Virus/pandemic	Diagnosis	Symptoms	Epidemiology	Treatment	Vaccine
H1N1	2009/04/25–2009/06/06	Week 6	293	80	82	122	170	139
COVID-19	2020/03/11–2020/04/22	Week 6	1,099	382	406	633	596	89
		Proportion	3.75	4.78	4.95	5.19	3.51	0.64
H1N1	2009/04/25–2009/06/13	Week 7	404	113	117	165	228	193
COVID-19	2020/03/11–2020/04/29	Week 7	1,512	494	527	827	829	109
		Proportion	3.74	4.37	4.50	5.01	3.64	0.56
H1N1	2009/04/25–2009/06/20	Week 8	463	122	127	189	262	218
COVID-19	2020/03/11–2020/05/06	Week 8	1,989	656	697	1,090	1,102	138
		Proportion	4.30	5.38	5.49	5.77	4.21	0.63
H1N1	2009/04/25–2009/06/27	Week 9	534	141	147	216	307	245
COVID-19	2020/03/11–2020/05/13	Week 9	2,502	830	879	1,355	1,388	161
		Proportion	4.69	5.89	5.98	6.27	4.52	0.66
H1N1	2009/04/25–2009/07/04	Week 10	582	158	165	240	330	262
COVID-19	2020/03/11–2020/05/20	Week 10	3,101	1,024	1,093	1,670	1,731	203
		Proportion	5.33	6.48	6.62	6.96	5.25	0.77

Each theme was individually analyzed and no exclusion was done using a specific theme as dominant. The data search was carried out using the PubMed (Public/Publisher MEDLINE) (https://pubmed.ncbi.nlm.nih.gov - Date - completion) for: (i) (swine flu OR H1N1 OR H1N1 influenza virus OR influenza virus OR H1N1 influenza OR H1N1/09 OR H1N1 virus OR A(H1N1)pdm09 OR H1N1 flu OR Mexican flu OR influenza A); (ii) (coronavirus disease-19 OR coronavirus disease OR corona virus OR COVID-19 OR COVID19 OR SARS-CoV-2); (iii) the descriptors of (i) and (ii) were used along with the following descriptors: (iiia) AND (diagnosis); (iiib) AND (symptoms); (iiic) AND (epidemiology); (iiid) AND (treatment); (iiie) AND (vaccine). Data extraction was carried out weekly for ten weeks after the WHO declared the swine flu (25th April 2009) and COVID-19 (11th March 2020) diseases as pandemic. Only published studies written in English (filter 1) and about Human species (filter 2) were evaluated.

Table 2 Types of publications for the studies about swine flu disease (2009) and COVID-19 (2020) disease ten weeks after the World Health Organization declared both diseases as pandemic.

Type of publication	H1N1		COVID-19	
	N	%	N	%
Case report	16	2.75	190	6.13
Comment	21	3.61	357	11.51
Letter	20	3.44	585	18.86
Editorial	25	4.30	495	15.96
Journal article	490	84.19	1,924	62.04
Comparative study	32	5.50	19	0.61
Observational study	0	0	20	0.64
Clinical study	32	5.50	30	0.97
Clinical trial	32	5.50	10	0.32
Clinical trial. Phase I	5	0.86	0	0
Clinical trial. Phase II	4	0.69	2	0.06
Clinical trial. Phase III	1	0.17	0	0
Clinical trial. Phase IV	0	0	0	0
Randomized controlled trial	26	4.47	7	0.23
Controlled clinical trial	26	4.47	7	0.23
Guideline	1	0.17	28	0.90
Review	85	14.60	307	9.90
Systematic review	6	1.03	22	0.71
Meta-analysis	1	0.17	16	0.52
Retracted publication	0	0	0	0
Retraction of publication	0	0	0	0

N, number of studies; %, percentage related to the total number of studies published after ten weeks of follow-up period. H1N1, Influenza A virus subtype H1N1; COVID-19; Coronavirus Disease 2019 (COVID-19). The types of studies were obtained from the PubMed database according to their classification.

about the risk factors related with the severity of the SARS-CoV-2 virus infection was higher than for H1N1 infection mainly regarding epidemiological data and/or comorbidities as risk factor for severe affection.[9–12] In addition, the number of clinical trials was greater for H1N1 pandemic, and the clinical trial (phase 2) during the first ten weeks of COVID-19 presented information about the use of Chloroquine Diphosphate as Adjunctive Therapy.[13] Also, in the first ten weeks after both pandemics were declared, no study was retracted. However, the Lancet journal retracted the study entitled ''Hydroxychloroquine or Chloroquine With or Without a Macrolide for Treatment of COVID-19: A Multinational Registry Analysis'' by Mehra et al.[14] and the Lancet editors expressed some concern about that study's data validity.[15]

The SARS-CoV-2 virus identification for COVID-19 was evidentiated in studies showing its limitations and highlights. However, it is necessary to optimize it to improve the applicability of this knowledge in several countries, such as Brazil, where the diagnostic test for SARS-CoV-2 is only carried out for severe cases of COVID-19.[4,16] Moreover, in the treatment area, the COVID-19 pandemic was associated with the hydroxychloroquine or chloroquine dilemma including divergencies between governments and the WHO; since hydroxychloroquine or chloroquine still has not been considered an efficient therapy for COVID-19 disease and the WHO discontinued the studies for these drug as COVID-19 therapy.[4,17–19] The epidemiology and symptoms were widely explored for COVID-19 pandemic and gave us the opportunity to understand the disease affection including cases with rare symptoms; moreover, the scientific community was able to determine the disease dissemination in a globalized world which facilitated the contamination between inhabitants from different countries and/or continents.[18,19] The vaccine until now is not available for SARS-CoV-2 virus infection, however, studies with good results were published and we hope to have a supply of vaccines as soon as possible.[18,20] Despite all limitations for better treatment for COVID-19, some discoveries highlight the importance of science, and among the important discoveries, it seems relevant to emphasize that in only four months the first randomized clinical trial with remdezivir was designed, conducted and published, proving that science can proceed very fast when under pressure.[21] Currently, there is a need for the valorization of science and the practical use of findings based on studies with greatest level of evidence and lowest risk of bias.

Brazilian scientists suffer from low financial support for science and the COVID-19 pandemic evidenced the low importance given by the government to this area. The Brazilian President favors popular beliefs to treat the disease, minimizing the risk of infection and the severity associated with this illness; however, this week the Brazilian President was diagnosed with SARS-CoV-2 infection. Brazilian scientists and health professionals wish the president a quick recovery and we trust that the scientific work will be better recognized regarding the efforts made to control the pandemic and to treat these patients.

In conclusion, science give us the knowledge to deal with situations such as the pandemics. However, in some countries, including Brazil, science should be better valued by the governments and the community. Special attention should be paid to the number of published studies hurriedly with low level of evidence and high risk of bias.[22] Readers should always evaluate the quality of each study and have a critical point of view to put into practice the knowledge acquired from the publications.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. [Accessed on 07th July 2020].
2. Secretarias de Saúde do Brasil. https://covid.saude.gov.br. [Accessed on 07th July 2020].
3. https://www.worldometers.info/coronavirus. [Accessed on 07th July 2020].
4. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020, http://dx.doi.org/10.1111/joim.13091. Online ahead of print.
5. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med. 2016;21:125–7, http://dx.doi.org/10.1136/ebmed-2016-110401.
6. Bergman D, Bethell C, Gombojav N, Hassink S, Stange KC. Physical distancing with social connectedness. Ann Fam Med. 2020;18:272–7, http://dx.doi.org/10.1370/afm.2538.
7. Malay DS. COVID-19, pandemic, and social distancing. J Foot Ankle Surg. 2020;59:447–8, http://dx.doi.org/10.1053/j.jfas.2020.03.010.
8. Machida M, Nakamura I, Saito R, Nakaya T, Hanibuchi T, Takamiya T, et al. Adoption of personal protective measures by ordinary citizens during the COVID-19 outbreak in Japan. Int J Infect Dis. 2020;94:139–44, http://dx.doi.org/10.1016/j.ijid.2020.04.014.
9. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS One. 2020;15:e0233147, http://dx.doi.org/10.1371/journal.pone.0233147.
10. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect. 2020;80(6):656–65, http://dx.doi.org/10.1016/j.jinf.2020.03.041.
11. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY). 2020;12:6049–57, http://dx.doi.org/10.18632/aging.103000.
12. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623, http://dx.doi.org/10.1016/j.tmaid.2020.101623.
13. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical Trial. JAMA Netw Open. 2020;3:e208857, http://dx.doi.org/10.1001/jamanetworkopen.2020.8857.
14. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020, http://dx.doi.org/10.1016/S0140-6736(20)31180-6. S0140-6736(20)31180-31186.
15. The Lancet Editors. Expression of concern: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020;395:e102, http://dx.doi.org/10.1016/S0140-6736(20)31290-3.
16. Marson FAL. One million cases of COVID-19: what have we learned? Rev Med (São Paulo). 2020;99(2):209–12, http://dx.doi.org/10.11606/issn.1679-9836.v99i2p209-212.
17. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020 [Epub Ahead of Print].
18. Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). J Microbiol Biotechnol. 2020;30:313–24, http://dx.doi.org/10.4014/jmb.2003.03011.
19. Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, et al. The epidemiology and clinical information about COVID-19. Eur J Clin Microbiol Infect Dis. 2020;39:1011–9, http://dx.doi.org/10.1007/s10096-020-03874-z.
20. Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Rep. 2020:1–4, http://dx.doi.org/10.1007/s40475-020-00201-6. Online ahead of print.
21. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569–78, http://dx.doi.org/10.1016/S0140-6736(20)31022-9.
22. Brainard J. Scientists are drowning in COVID-19 papers. Can new tools keep them afloat? Posted in: Scientific Community. doi:https://doi.org/10.1126/science.abc7839.

Pulmonol. 2020;**26(6)**:346–352

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Disseminated Bacillus Calmette-Guérin (BCG) infection with pulmonary and renal involvement: A rare complication of BCG immunotherapy. A case report and narrative review

Marta Marques*, Dolores Vazquez, Susana Sousa, Gonçalo Mesquita, Maria Duarte, Rosa Ferreira

Serviço de Medicina Interna, Centro Hospitalar Póvoa de Varzim/Vila do Conde, Portugal

Received 12 September 2019; accepted 4 October 2019

KEYWORDS
Bacillus Calmette-Guérin (BCG) immunotherapy;
Disseminated BCG infection;
BCGitis;
Nephritis;
Pneumonitis;
Miliary tuberculosis

Abstract Intravesical Bacillus Calmette-Guérin (BCG) instillation is a mainstay of adjunctive therapy for superficial bladder cancer that increases length of disease progression-free survival. Although usually well tolerated, moderate to severe local and systemic infectious complications can occur with this immunotherapy. Diagnosis is difficult and often based on high clinical suspicion since in many cases *Mycobacterium bovis* is not isolated. Treatment is not fully standardized but the combination of anti-tuberculosis drugs and corticosteroids is advocated in severe cases.

The authors present an unusual case of a severe infectious complication following intravesical BCG instillation with pulmonary and kidney involvement. Prompt anti-tuberculosis treatment associated to corticosteroid resulted in a marked clinical and radiological improvement, supporting the diagnosis of disseminated BCG infection. Based on this, the authors aimed to review the literature on this exceptional complication of this immunotherapy.

Introduction

Intravesical instillation of bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, is an efficient immunotherapy for superficial bladder cancer, which is associated with increased length of disease progression-free survival.[1] The BCG therapy is usually well tolerated, with some minor side effects reported, generally self-limiting without specific treatment.[2]

Serious adverse events are uncommon (less than 5%) and are usually related to disseminated BCG infection (<1%).[3] Its diagnosis is challenging since at least half of the cases do not

* Corresponding author.
E-mail address: msmarques@chpvvc.min-saude.pt (M. Marques).

https://doi.org/10.1016/j.pulmoe.2019.10.001

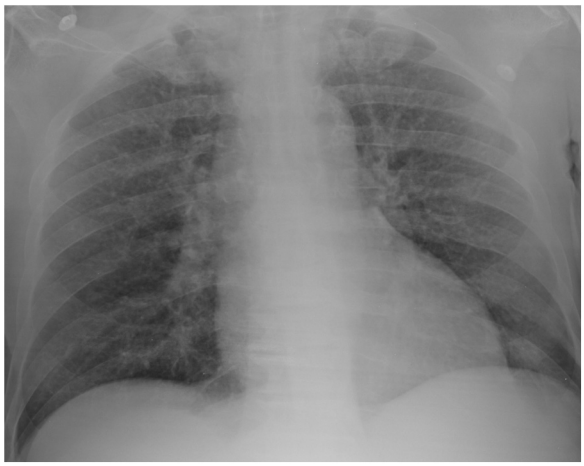


Figure 1 Chest radiograph on admission showing a diffuse opacities and nodules.

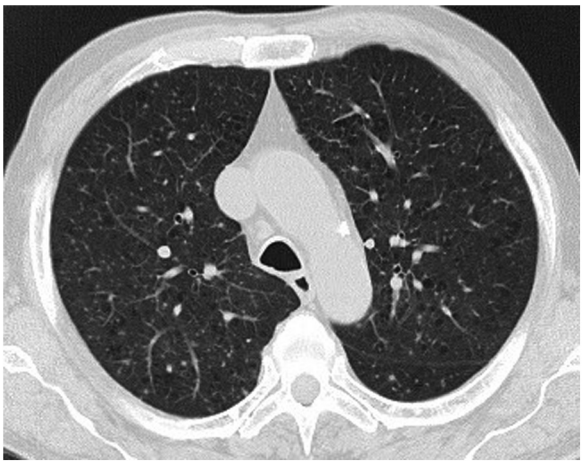


Figure 2 Thoracic CT scan showing pulmonary nodules in a miliary pattern.

yield positive microbiological results.[1,4] Sepsis is its most fulminant manifestation but infection of several organs, such as the liver or the bone, can arise. Pulmonary involvement is very rare (0.3–0.7% of the cases), usually presenting as interstitial pneumonitis or miliary dissemination.[5]

In this manuscript, we report a rare case of a patient with a disseminated infection with pulmonary involvement after BCG intravesical instillation, and conduct a narrative review of the literature on this topic.

Case report

A 69-year-old man, with history of hypertension and dyslipidemia, was diagnosed with high-grade bladder urothelial carcinoma (pT1). A transurethral resection of the bladder was performed, followed by mensal BCG intravesical instillation in the last 18 months, without major adverse reactions except flu-like symptoms lasting less than 48 h after each dose. Two days after the last instillation, he presented macroscopic hematuria and severe fatigue, sweating and persistent non-productive cough. Eight days later, due to the persistence of symptoms and the appearance of dyspnea and fever, he went to the emergency department. He had no recent sick or tuberculosis contacts. On admission, he was febrile (38.3 °C), hypotensive (89/40 mmHg), in respiratory distress with inspiratory crackles in both lungs. Arterial blood gas analysis showed, in ambient air, hypoxemia [partial pressure of oxygen 63 mmHg) and respiratory alkalosis. Laboratory tests revealed mild anemia (hemoglobin 11.9 g/dL) with normal white blood cell and platelet count, increased levels of C-reactive protein (10.9 mg/dL) and erythrocyte sedimentation rate (57 mm/h), acute kidney injury [serum creatinine (sCr) 2.35 mg/dl], hematuria, leukocyturia and proteinuria. Serological tests were negative for hepatitis B and C and human immunodeficiency virus. Markers of immune-mediated disease (antinuclear, antineutrophil cytoplasmic, antiglomerular basement membrane and anti-streptolysin O antibodies) were all negative. Serum immunoglobulins and complement levels were normal. The chest radiography showed a bilateral reticulonodular infiltrate (Fig. 1) and the thoracic computed tomography (CT) demonstrated a diffuse pulmonary micronodulation, in a miliary pattern (Fig. 2). Renal ultrasonography revealed normal-sized kidneys with a reduced corticomedullary differentiation. Specimens for microbiological exam were collected and empirical broad-spectrum antibiotic treatment was started. On the fifth day of treatment, both fever and acute respiratory failure persisted, lung opacities were unmodified and renal function worsened (sCr 3.52 mg/dL). Multiple cultures of sputum, urine and blood were negative for both bacteria and mycobacteria, including polymerase chain reaction (PCR). A bronchoscopy with bronchoalveolar lavage (BAL) was performed which revealed a prevalence of lymphocytes (48.2%) and an elevated CD4/CD8 ratio (11), absence of malignant cells and bacteriological and mycobacteriological exams were negative. Due to the lack of clinical and imagiological improvement, the diagnosis of disseminated BCG infection was suggested and empiric antituberculosis treatment (ATT) [isoniazid 300 mg, rifampin 600 mg and ethambutol 1200 mg; once daily] associated with a corticosteroid (prednisolone 60 mg once daily) was started and, few days later, patient's clinical condition improved, with sustained apyrexia, resolution of acute respiratory failure and slow but steady recovery of renal function. He was discharged in good general condition and continued ATT for 6 months. Steroids were discontinued tapering down the dosage for 5 months. A high-resolution CT scan of thorax, performed 6 months after discharge, showed almost complete resolution of the lung opacities with a reduction in the number and size of bilateral pulmonary nodules (Fig. 3) and kidney function was fully recovered (sCr 0.86 mg/dL). BCG immunotherapy was discontinued. No sign of relapse was observed after one year of follow-up.

Discussion

BCG immunotherapy provides the best risk-benefit therapy in patients with high-risk superficial bladder cancer and isthe most commonly used and effective adjunctive therapy for this malignancy.[2] Several studies have shown that intravesical BCG is more effective than intravesical chemotherapy.[6] BCG infusions promote an immunomodu-

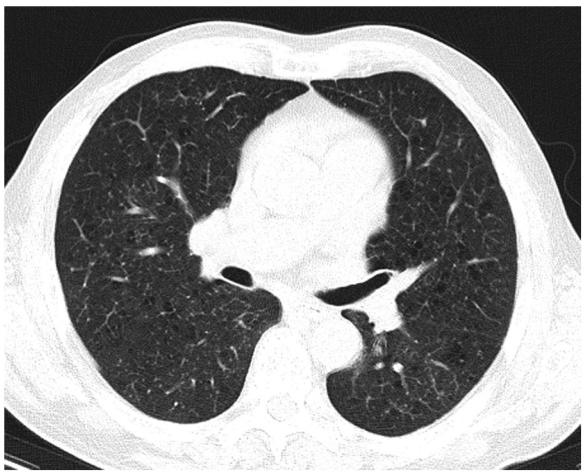


Figure 3 The high-resolution CT scan of thorax performed 6 months after discharge showed a marked reduction in the number and size of bilateral pulmonary nodules.

latory process characterized by a local immune activation involving a multitude of cytokines and local migration of polymorphonuclear cells, ultimately leading to the death of tumor cells.[7] Due to this inflammatory challenge, minor side effects are commonly reported including genitourinary symptoms, such as cystitis (91%), macroscopic hematuria (1%), bladder contracture (0,2%), granulomatous prostatitis (0,9%), epididymo-orchitis (0,4%) and urethral obstruction (0,3%). Low-grade fever, malaise and chills following instillation are also common and usually self-limiting within a few hours or days.[3,7] Serious adverse events were reported in less than 5% of over 2600 patients treated with BCG instillations, which include pneumonitis or hepatitis (0,7%), cytopenia (0,1%) and sepsis (0,4%).[3] Similar results were described in a pooled analysis of case reports[8] and in a recent retrospective review[9] that revealed an incidence of BCG infection of 4.3% and 1.3%, respectively.

Disseminated BCG infection, also referred as BCGitis , should be suspected in any patient who develops moderate-to-severe genitourinary or systemic symptoms, following $\geq$1 instillation of intravesical BCG, responding to ATT and with no alternative diagnosis. Microbiologic or histopathologic evidence of mycobacterial infection is not necessary for diagnosis.[8]

In our patient, dissemination of *M. bovis* developed following an intravesical BCG instillation. Although mycobacterial identification was not achieved, a presumptive diagnosis of disseminated BCG was justified by the clinical presentation consistent with active tuberculosis, associated with radiological findings consistent with pulmonary spread of *M. bovis*. Additionally, the evidence of macroscopic hematuria and acute kidney injury suggested an initial regional effect with generalized BCGitis coursed with pneumonitis.

The lack of mycobacterial identification is not unusual since, as pointed out by a recent review, serological tests and cultures are negative in approximately 60% of cases, being useful especially for differential diagnosis.[8] The exclusion of an alternative diagnosis and the prompt response to treatment should be considered the cornerstones of BCGitis diagnosis, as we observed in our patient.

Risk factors for disseminated infection include host characteristics, such as the extent of bladder mucosal damage and immunodeficiency, which are considered more important than therapeutic regimen features.[8,10] Our patient received 18 BCG instillations without major complications but this repeated exposure may have predisposed him to subsequent dissemination, although dissemination can occur at any time in the course of treatment.[8] Interestingly, all reported cases of disseminated BCG infection treated with BCG immunotherapy occurred in males, suggesting a potential influence of sex hormones in this susceptibility.[11]

Pulmonary involvement is very rare and can present as hypersensitivity or mycobacterial pneumonia. Hypersensitivity is usually characterized by an interstitial pattern in chest x-ray and lymphocytosis on BAL.[12] Miliary pattern nodules in lung parenchyma is rarely reported in the literature. An extensive and systematic review of the literature, retrieved 26 published cases[11–36] (Table 1) which provide a comprehensive clinical, radiological and microbiological information of miliary tuberculosis caused by disseminated BCG infection in adults treated with intravesical BCG immunotherapy.

The diagnosis can be confirmed by the presence of epithelio-giganto-cellular granulomas with or without caseous necrosis in bronchial or pulmonary biopsy. However, since they are present in only 40% of biopsies, in most of the cases they do not contribute to the diagnosis.[37] As previously reported, caseous necrosis is usually absent (Table 1). Pulmonary parenchymal changes also include fibrosis of the lung and lymphocytic alveolar infiltrates consistent with hypersensitivity alveolitis. BAL cellular profile usually shows lymphocytosis with an elevated CD4/CD8 ratio consistent with a T helper alveolitis,[38] as we documented in our patient.

Although its pathogenesis is not fully understood, some authors believe that BCGitis is caused by hypersensitivity reactions and the granulomas are due to type 4 hypersensitivity reaction and not infection, supported by the negative results of cultures and of serological and molecular tests, along with successful response to steroids.[12,22–24,35,36] On the other hand, some case reports support the theory of an ongoing active BCG infection demonstrated by the presence of viable bacilli inside the lesions[16] or detection of mycobacterial genome by Polymerase Chain Reaction assays,[11,26,27,30,34] that require specific treatment. This supports the absence of a standardized treatment for BCG complications.

In our case, it can be argued that patient's symptoms were due to hypersensitivity reaction, because of negative culture results from BAL as well as absence of acid-fast bacilli on direct microscopy, and also the BAL cellular profiles revealed lymphocytosis with an elevated CD4/CD8 ratio. However, due to the persistence and severity of clinical symptoms with respiratory failure, antituberculous were added to steroids with clinical improvement within 3 days. The speed of improvement suggests the more important role of hypersensitivity rather than infection.

Until now, trials done have not been good enough to determine the most effective treatment. In addition, in some case reports, simple discontinuation of BCG alone was sufficient. Venn et al. illustrated a case who had febrile illness for more than one month with persisting pulmonary nodules, that improved without any treatment. The authors

Table 1 Published cases of miliary tuberculosis caused by disseminated BCG infection in adults treated with intravesical BCG immunotherapy.

Patient, reference	Journal, study design	Age, gender	Symptoms	No. of BCG instillations	Pathological findings	Microbiological diagnosis	Treatment; duration (months)	Outcome
1, Gupta et al., 1988 [13]	*Chest;* CR	78, M	Fever, cough	10	NCG	All negative	INH, RIF, EMB (9)	Resolution
2, Kesten et al., 1990 [14]	*Thorax*; CR	67, M	Fever, weight loss	4	NCG	All negative	INH, RIF NS	Resolution
3, Baloira Villar et al., 1992 [15]	*Med Clin (Barc);* CR	78, M	Fever, weight loss,haemoptysis	5	CG	Acid fast stain	INH, RIF, PZA (6)	Resolution
4, McParland et al., 1992 [16]	*Am Rev Respir Dis;* CR	69, M	Fever, chills, cough	6	NCG	Culture *M.bovis* (lung biopsies)	INH, RIF, PZA, STM, steroids; (12)	Resolution
5, Smith et al., 1993 [17]	*Cancer;* CR	69, M	Asymptomatic	6	CG	All negative	INH, RIF, PZA NS	Death
6, Palayew et al., 1993 [18]	*Chest;* CR	57, M	Weight loss, cough, dyspnea	10	NCG	Acid fast stain	INH, RIF,EMB steroids; (9)	Resolution
7, Jasmer et al., 1996 [19]	*Radiology*; CR	73, M	Fever, weight loss	9	CG	All negative	INH, RIF, EMB (9)	Resolution
8, Paredes et al., 1996 [20]	*Arch Bronconeumol;*CR	67, M	Fever, chills	14	CG	All negative	INH, RIF, EMB NS	Death
9, Iantorno et al., 1998 [21]	*J Uro*; CR	79, M	Fever, chills, cough, dyspnea	8	NCG	All negative	INH, RIF, EMB PZA; NS	Resolution
10, Rabe et al., 1999 [22]	*AJR Am J Roentgenol;* CR	60, M	Fever, malaise, arthralgias	16	NCG	All negative	INH, RIF, EMB steroids; (3)	Resolution
11, Elkabani et al., 2000 [23]	*Cancer Control;* CR	67, M	Fever, weakness, dyspnea	16	ND	All negative	INH, RIF, LEV steroids; (12)	Resolution
12, Audigier et al., 2000 [24]	*Rev Mal Respir;* CR	69, M	Fever, dyspnea	5	NCG	All negative	INH, RIF steroids; (9)	Resolution
13, Mignon et al., 2002 [25]	*J Radiol;* CR	76, M	Fever	10	ND	All negative	INH, RIF, EMB (6)	Resolution
14, Toscano et al., 2003 [26]	*Eur J Clin Microbiol Infect Dis;* CR	72, M	Fever, weight loss, cough	6	NS	PCR *M. tuberculosis complex*	INH, RIF, EMB steroids; (12)	Resolution
15, Castillo et al., 2006 [27]	*Med Intensiva*; CR	75, M	Fever, dyspnea	NS	Diffuse inflammator signs	PCR *M. tuberculosis complex* (BAL)	INH, RIF, EMB steroids; NS	Death
16, Nadasy et al., 2008 [28]	*South Med J;* CR	62, M	Fever, malaise, cough	3	CG	Acid fast stain	INH, RIF, LEV steroids; (6)	Resolution
17, Cobas Paz et al., 2010 [29]	*Arch Bronconeumol;*CR	62, M	Asymptomatic	6	NCG	All negative	INH, RIF, EMB (6)	Resolution

Table 1 (*Continued*)

Patient, reference	Journal, study design	Age, gender	Symptoms	No. of BCG instillations	Pathological findings	Microbiological diagnosis	Treatment; duration (months)	Outcome
18, Colmenero et al., 2012 [30]	*Diagn Microbiol Infect Dis; CR* and Review	56, M	Fever, chills, malaise, cough	9	ND	PCR *M. tuberculosis complex* (BAL)	INH, RIF steroids; (9)	Resolution
19, Caramori et al., 2013 [11]	*Monaldi Arch Chest Dis;* CR and Review	66, M	Fever, dyspnea	18	NCG	PCR *M. tuberculosis complex* (BAL)	INH, RIF, EMB PZA, steroids; (9)	Resolution
20, Choi CR et al., 2014 [31]	*BMJ Case Rep;* CR	51, M	Weakness, weight loss	5	NCG	All negative	INH, RIF, EMB NS	Resolution
21, Venn et al., 2014 [32]	*BMJ Case Rep;* CR	74, M	Fever, night sweats, anorexia	7	ND	All negative	None	Resolution
22, Rosati et al., 2016 [12]	*Urologia;* CR	63, M	Fever, cough	6	NCG	All negative	INH, RIF, EMB steroids; (9)	Resolution
23, Smith et al., 2016 [33]	*BMJ Case Rep;* CR	69, M	Cough, night sweats, weight loss	NS	ND	All negative	INH, RIF, EMB (9)	Resolution
24, Calleris et al., 2017[34]	*Le Infezioni in Medicina;* CR	73, M	Fever, weakness, night sweats	NS	ND	PCR *M. tuberculosis* (sputum)	INH, RIF, EMB NS	Resolution
25, Kaburaki et al., 2017[35]	*Intern Med;* CR	62, M	Fever, fatigue	8	NCG	All negative	INH, RIF, EMB steroids; (9)	Resolution
26, Clérigo et al., 2019[36]	*Acta Med Port*; CR	67, M	Fever	6	NCG	All negative	INH, RIF, EMB steroids; (12)	Resolution

Abbreviations: BALBronchoalveolar cultures; CGCaseating granuloma; CRcase report; EMBEthambutol; INHIsoniazid; LEVLevofloxacin; Mmale; NCGNoncaseating granuloma; NSNot specified; NDNot done; PCRpolymerase chain reaction; PZAPyrazinamide; RIFRifampin; STMStreptomycin. [Obtained with the data from Refs.[10–33]

suggested that some pulmonary reactions, with mild initial presentation, may resolve spontaneously, whether due to hypersensitivity or natural clearance of BCG.[32]

Nevertheless, in disseminated BCG infection, the combination of antimycobacterial therapy and corticosteroids is suggested.[3] *M. bovis* is inherently resistant to pyrazinamide and cycloserine, so a regimen that includes isoniazid and rifampin for 6 months with ethambutol for 2 months can be used. When liver toxicity is a concern, regimens including ethambutol, fluoroquinolones and amikacin have been proposed. The corticosteroid adjuvant therapy is particularly important where there is extensive miliary involvement and respiratory failure, but until now, no standardized regimen has been recommended.[8] A retrospective review of eight cases revealed improvement with just steroid treatment in patients with clinical signs of hypersensitivity, including pneumonitis and hepatitis.[39]

Since no routine prophylaxis protocol has demonstrated long-term efficacy for systemic BCG infection prevention,[32] most authors consider a previous systemic BCG infection a contraindication to restarting immunotherapy.[9]

The prognosis seems to be favourable in most patients when an appropriate therapy is started. Pérez-Jacoiste Asín et al.[8] observed a 5,4% attributable mortality, generally due to respiratory, liver and multiple organ failure.

This case highlights the importance of recognizing disseminated BCG infection as a potential complication in patients with previous BCG exposure, but more studies are necessary not only to fully understand its pathogenesis but also to standardize the diagnosis and treatment.

References

1. Lamm DL. Efficacy and safety of Bacille Calmette-Guérin immunotherapy in superficial bladder cancer. Clin Infect Dis. 2000;31(3):S86–90.
2. Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK. BCG intravesical instillations: recommendations for side-effects management. Eur Urol. 2000;37(1):33–6.
3. Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol. 1992;147:596–600.
4. Dammert P, Boujaoude Z, Rafferty W, Kass J. Fever of unknown origin and pancytopenia caused by culture-proven delayed onset disseminated bacillus Calmette-Guérin (BCG) infection after intravesical instillation. BMJ Case Rep. 2013:10–2.
5. Calleris G, Marra G, Corcione S, Oderda M, Cardellino C, Audagnotto S, et al. Miliary pulmonary infection after BCG intravesical instillation: a rare, misdiagnosed and mistreated complication. Infez Med. 2017:366–70.
6. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette–Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004;93:485–90.
7. Thompson DB, Siref LE, Feloney MP, Hauke RJ, Agrawal DK. Immunological basis in the pathogenesis and treatment of bladder cancer. Expert Rev Clin Immunol. 2015;11(2):265–79.
8. Pérez-Jacoiste Asín MA, Fernández-Ruiz M, López-Medrano F, Lumbreras C, Tejido A, San Juan R, et al. Bacillus Calmette-Gérrin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer. Medicine. 2014;93:236–54.
9. González-Del Vecchio M, Ruíz-Serrano MJ, Gijón P, Sánchez-Somolinos M, Egea V, García de Viedma D, et al. Differences between a probable and proven BCG infection following intravesical instillations: 16 years experience in a tertiary care hospital. Diagn Microbiol Infect Dis. 2016;85(3):338–43.
10. Brausi M, Oddens J, Sylvester R, Bono A, van de Beek C, van Andelr G, et al. Side effects of bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomized phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol. 2014;65(1):69–76.
11. Caramori G, Artioli D, Ferrara G, Cazzuffi R, Pasquini C, Libanore M, et al. Severe pneumonia after intravesical BCG instillation in a patient with invasive bladder cancer: case report and literature review. Monaldi Arch Chest Dis. 2013;79(1):44–8.
12. Rosati Y, Fabiani A, Taccari T, Ranaldi R, Mammana G, Tubaldi A. Intravesical BCG therapy as cause of miliary pulmonary tuberculosis. Urologia. 2016;83(1):49–53.
13. Gupta RC, Lavengood R Jr, Smith JP. Miliary tuberculosis due to intravesical bacillus Calmette–Guérin therapy. Chest. 1988;94:1296–8.
14. Kesten S, Title L, Mullen B, Grossman R. Pulmonary disease following intravesical BCG treatment. Thorax. 1990;45:709–10.
15. Baloira Villar A, Agüero Balbín R, Bustamante Ruiz A, Jiménez Gómez A. Miliary tuberculosis secondary to intravesical instillation of Calmette–Guerin bacilli. Med Clin (Barc). 1992;99:158.
16. McParland C, Cotton DJ, Gowda KS, Hoeppner VH, Martin WT, Weckworth PF. Miliary Mycobacterium bovis induced by intravesical bacille Calmette–Guérin immunotherapy. Am Rev Respir Dis. 1992;146:1330–3.
17. Smith RL, Alexander RF, Aranda CP. Pulmonary granulomata: a complication of intravesical administration of bacillus Calmette–Guérin for superficial bladder carcinoma. Cancer. 1993;71:1846–7.
18. Palayew M, Briedis D, Libman M, Michel RP, Levy RD. Disseminated infection after intravesical BCG immunotherapy: detection of organisms in pulmonary tissue. Chest. 1993;104:307–9.
19. Jasmer RM, McCowin MJ, Webb WR. Miliary lung disease after intravesical bacillus Calmette–Guérin immunotherapy. Radiology. 1996;201:43–4.
20. Paredes Arranz C, Frutos Arribas JF, Calleja Escudero J, Blanco Cabero M, Campo Matías F, Velasco MC. Miliary dissemination with pulmonary involvement secondary to intravesical immunotherapy with Calmette–Guérin bacillus. Arch Bronconeumol. 1996;32:100–2.
21. Iantorno R, Nicolai M, Storto ML, Ciccotosto C, Cipollone G, Mastroprimiano G, et al. Miliary tuberculosis of the lung in a patient treated with bacillus Calmette–Guerin for superficial bladder cancer. J Urol. 1998;159:1639–40.
22. Rabe J, Neff KW, Lehmann KJ, Mechtersheimer U, Georgi M. Miliary tuberculosis after intravesical bacille Calmette–Guérin immunotherapy for carcinoma of the bladder. AJR Am J Roentgenol. 1999;172:748–50.
23. Elkabani M, Greene J, Vincent A, Vanhook S, Sandim R. Disseminated mycobacterium bovis after intravesicular bacillus calmette-Guérin treatments for bladder cancer. Cancer Control. 2000;7(5):476–81.
24. Audigier C, Nesme P, Perol M, Guerin JC. Rare pulmonary complication in intravesical BCG treatment. Rev Mal Respir. 2000;17:679–81.
25. Mignon F, Chevri re A, Mesurolle B, El Hajam M, Morel H, Lacombe P. Miliary induced by intravesical BCG immunotherapy for carcinoma of the bladder: CT findings. J Radiol. 2002;83:368–71.
26. Toscano Rico M, Machado J, Cardoso O, Salvado C, Rodrigues P, Proença R. Severe disseminated tuberculosis after intravesi-

cal instillation of Bacillus Calmette-Guérin. Eur J Clin Microbiol Infect Dis. 2003;22(7):447–8.
27. Del Castillo Duran Y, Santos Bodí F, Castander Serentill D, Jubert Montaperto P, Espinosa Valencia P, Rabassó Sole C. Tuberculosis miliar in a patient treated with intravesical instillations of bacillus Calmette-Guérin. Med Intensiva. 2006;30(3): 116–9.
28. Nadasy KA, Patel RS, Emmett M, Murillo RA, Tribble MA, Black RD, et al. Four cases of disseminated Mycobacterium bovis infection following intravesical BCG instillation for treatment of bladder carcinoma. South Med J. 2008;101(1):91–5.
29. Cobas Paz A, García Tejedor JL, González Piñeiro A, Fernández-Villar A. Miliary tuberculosis due to BCG in an asymptomatic patient: initial onset or a condition not yet described? Arch Bronconeumol. 2010;46:394–5.
30. Colmenero JD, Sanjuan-Jimenez R, Ramos B, Morata P. Miliary pulmonary tuberculosis following intravesical BCG therapy: case report and literature review. Diagn Microbiol Infect Dis. 2012;74:70–2.
31. Choi CHR, Lee SO, Smith G. Subclinical miliary Mycobacterium bovis following BCG immunotherapy for transitional cell carcinoma of the bladder. BMJ Case Rep. 2014;2014, bcr-3013-201202.
32. Venn RM, Sharma N. Resolution without treatment of granulomatous pneumonitis due to intravesical BCG for bladder cancer. BMJ Case Rep. 2014:1–3.
33. Smith DM. BCG-osis following intravesical BCG treatment leading to miliary pulmonary nodules, penile granulomas and a mycotic aortic aneurysm. BMJ Case Rep. 2016, bcr-2016-215635.
34. Calleris G, Marra G, Corcione S, Oderda M, Cardellino C, Audagnotto S, et al. Miliary pulmonary infection after BCG intravesical instillation: a rare, misdiagnosed and mistreated complication. Le Infezioni in Medicina. 2017;(4):366–70.
35. Kaburaki K, Sugino K, Sekiya M, Takai Y, Shibuya K, Homma S. Milliary tuberculosis that developed after intravesical Bacillus Calmette-Guerin therapy. Intern Med. 2017;(56):1563–7.
36. Clérigo V, Castro A, Mourato T, Gomes C. A rare case of granulomatous Pneumonitis due to intravesical BCG for bladder cancer. Acta Med Port. 2019;32(4):316–20.
37. Attou R, Albrich T, Kadou J, Redant S, Honoré PM, De Bels D. Favorable outcome in a patient with systemic BCGitis after intra-bladder instillation of Calmette-Guerin bacillus highlighting the importance of making the correct diagnosis in this rare form of sepsis. J Transl Int Med. 2019;7(1):34–8.
38. Namen AM, Grosvenor AR, Chin R, Daybell D, Adair N, Woodruff RD, et al. Pulmonary infiltrates after intravesical Bacille Calmette-Guerin: two cases and review of the literature. Clin Pulmon Med. 2001;8(3):177–9.
39. Gonzalez OY, Musher DM, Brar I, et al. Spectrum of Bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. Clin Infect Dis. 2003;36(2):140–8.

Pulmonol. 2020;**26(6)**:353–362

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Host factors associated to false negative and indeterminate results in an interferon-γ release assay in patients with active tuberculosis

J.A. Santos[a,b,*], **R. Duarte**[c,d], **C. Nunes**[a]

[a] *NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa, Portugal Avenida Padre Cruz, 1600-560 Lisboa, Portugal*
[b] *National Health Institute Dr. Ricardo Jorge, Portugal Avenida Padre Cruz, 1600-560 Lisboa, Portugal*
[c] *Chest Disease Center, Vila Nova de Gaia, Portugal Rua Conselheiro Veloso da Cruz, 4400-092 Vila Nova de Gaia, Portugal*
[d] *Faculdade de Medicina da Universidade do Porto, Portugal Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal*

Received 19 September 2019; accepted 11 November 2019
Available online 13 December 2019

KEYWORDS
Tuberculosis;
Interferon-gamma release tests;
Tuberculin test;
Public health;
Latent tuberculosis;
Preventive medicine

Abstract
Introduction: Information on host factors that contribute to false negative and indeterminate results in interferon-γ release assays (IGRA) are critical to improve the usefulness of these tests in the fight against tuberculosis (TB) epidemics.

The aim of this study was to estimate and compare the sensitivity of an IGRA and the tuberculin skin test (TST), independently and as a combined approach, in patients with TB and to identify risk factors associated with false negative and indeterminate IGRA results.
Methods: Retrospective cohort study of all active TB notifications with an IGRA result (n = 1230), from 2008 to 2015. 68.0 % (n = 727) of these patients had a TST result interpreted using a 5 mm (TST-5 mm) and 10 mm (TST-10 mm) cutoff. Sensitivity was determined for both tests.

Logistic regression analysis was used to evaluate the association of sociodemographic and clinical factors to the risk of false negative or indeterminate IGRA results.
Results: IGRA, TST-5 mm and TST-10 mm were positive in 82.4 %, 84.5 % and 78.4 % of the patients that performed both tests. When used combined, IGRA/TST-5 mm sensitivity was 91.7 % and IGRA/TST-10 mm sensitivity was 90.6 %. Age≥65 years, alcohol abuse and pulmonary TB were predictive factors for indeterminate results. Inflammatory diseases and pulmonary TB were statistically associated with false negative IGRA results.

* Corresponding author at: Epidemiology and Statistics Department, Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, Avenida Padre Cruz, 1600-560 Lisboa, Portugal.
E-mail addresses: jpa.santos@outlook.pt (J.A. Santos), raquelafduarte@gmail.com (R. Duarte), cnunes@ensp.unl.pt (C. Nunes).

https://doi.org/10.1016/j.pulmoe.2019.11.001

Conclusion: Inflammatory diseases and pulmonary TB were identified as factors for false negative IGRA results. Our results indicate that the use of both tests in a combined approach, especially in specific risk groups of the population, could increase the sensitivity of the screening process and accelerate the achievement of the WHO End TB Strategy goals.

Introduction

The timely identification of latent tuberculosis infection (LTBI) cases and implementation of preventive treatment can substantially decrease the risk of people developing tuberculosis (TB) disease from a latent infection and, consequently, reduce TB-related morbidity and mortality, reduce transmission, and the burden of the disease.[1]

The existing screening tests are indirect methods that only provide immunological evidence of host sensitization to *Mycobacterium tuberculosis* antigens, do not differentiate accurately between LTBI and active TB or provide evidence regarding the stage and potential progression from infection to disease.[2]

WHO guidelines recommend the use of the tuberculin skin test (TST) and the interferon-γ release assays (IGRA) as screening tests.

IGRAs measure T-cell release of interferon-γ in response to stimulation by two strongly immunogenic but highly specific *M. tuberculosis* complex antigens (ESAT-6 and CFP-10). Two IGRAs are commercially available, QuantiFERON-TB Gold assay (Qiagen) and the T-SPOT.*TB* assay (Oxford Immunotec), both detecting the release of interferon-γ in response to the specific *M. tuberculosis* antigens through different methods.

IGRAs have higher specificity for *M. tuberculosis* than the TST, as the antigens used are not encoded in the genomes of any of the BCG vaccine strains or most species of non-tuberculous mycobacteria.[3] Furthermore, these tests have logistic advantages when compared to TST (e.g. require only one visit), have positive and negative controls (e.g. identification of potential cases of anergy), and no boost effect when repeated.[2]

However, these assays are more expensive and require laboratory infrastructure. Also, T-cell assays such as IGRA are susceptible to variability by different factors at multiple levels, including assay manufacturing, preanalytical processing (e.g. blood volume, sample transport temperature, incubation time) or analytical testing.[3]

IGRAs have shown reduced sensitivity in immunocompromised patients, especially in those with a severe immune depression, such as patients with diabetes[4] or HIV infection.[5] IGRAs have also presented a lower sensitivity in young (<5years of age) or immunocompromised children.[6,7]

Another drawback of IGRA testing is the occurrence of indeterminate results, which may result from an insufficient immune response to the positive control or a high level of response in the negative control,[8] with previous studies presenting rates of indeterminate IGRA results ranging between 2 % and 11 %.[8]

In order to improve the usefulness of the IGRAs as a diagnostic aid for detection of LTBI, it is essential to better understand which factors are associated with false negative and indeterminate IGRA results.

Since there is no diagnostic gold standard for LTBI to help evaluate the IGRAs, sensitivity can be estimated using surrogate reference standards such as IGRA results from patients with a definitive TB diagnosis and, through collected epidemiological data, determine factors that may be associated with false negative results.

The objective of this study was to analyse the performance of an IGRA test in patients with active TB. The specific objectives were to: (i) determine and compare the sensitivity of IGRA and TST tests; (ii) search for risk factors that could be linked with indeterminate IGRA results; and (iii) ascertain risk factors that could be associated with false negative IGRA results.

Material and methods

Study design and data source

Retrospective cohort study centered on data from active TB cases notified in the Portuguese National Tuberculosis Surveillance System (SVIG-TB), from 2008 to 2015. This official database is generated by direct compulsory reporting by health care providers and the data from this official system of notification is complemented and updated during TB cases follow-up. Patients notified in the database are diagnosed based on laboratory confirmed TB (through identification of *M. tuberculosis* by microscopy, cultural and/or molecular methods) and/or based on clinical and radiological findings and a favorable TB treatment response.

For this study ethics committee approval or informed consent was not required, as all patient's information retrieved from the SVIG-TB database was fully anonymized.

Study data

The study included all patients notified in the SVIG-TB database with an IGRA test result. The IGRA test used in the patients enrolled in the study was the QuantiFERON-TB Gold In-Tube (Qiagen).

The clinical and sociodemographic variables analyzed were sex, age group, comorbidities (chronic renal failure in dialysis, oncologic diseases, inflammatory diseases, HIV infection, chronic obstructive pulmonary disease [COPD] and diabetes), substance abuse (alcohol and drug abuse) and site of disease (pulmonary or extrapulmonary TB). IGRA and

TST results were the dependent variable (event: negative results).

Indeterminate IGRA results were assessed by dividing the results into determinate (positive and negative results) and indeterminate (event).

Statistical analysis

TST induration measurements were interpreted using two cutoff points, ≥5 mm (TST-5 mm) and ≥10 mm (TST-10 mm),[9] and converted to positive or negative results.

Results from patients that underwent both diagnostic tests were used to calculate the sensitivity with 95 % confidence interval for each test separately and in combination (IGRA/TST-5 mm or IGRA/TST-10 mm). Sensitivity outcomes were compared using McNemar's test.[10]

Bivariate and multivariate logistic regression analysis[10] was used to determine the variables that were significantly associated with the occurrence of indeterminate and false negative IGRA results. Multivariate logistic regression analysis with forward stepwise (Likelihood Ratio) method, logit function (entry-0.05; removal-0.10), included variables that were significant in bivariate analyses. Odds ratio were reported with 95 % confidence intervals (95 %CI). Statistical analyses were performed using IBM® SPSS® Statistics for Windows, version 23 (IBM Corp., N.Y., USA).

Results

There were 1230 patients notified with active TB in the SVIG-TB database (2008–2015) with an IGRA test, 857 patients (69.7 %) had a positive test result, 212 (17.2 %) had a negative result and 161 (13.1 %) had an indeterminate result. Among the 1069 patients with a determinate IGRA result, 727 (68.0 %) also had a TST result.

The mean (±standard deviation) age of the patients with a determinate IGRA result (n = 1069, 86.9 %) was 47.9 (±20.0), ranging from less than 1 to 91 years. Portugal was the main country of origin (n = 931; 87.1 %), followed by Angola (n = 31, 2.9 %), Cabo Verde (n = 23, 2.2 %), Guinea-Bissau (n = 19, 1.8 %) and Mozambique (n = 12, 1.1 %).

Diabetes mellitus was the most common comorbidity and chronic renal failure was the least frequent.

IGRA and TST sensitivity

Considering the patients who performed IGRA and TST assays (n = 727), overall sensitivity was 82.4 %, 84.6 % and 78.4 % for IGRA, TST-5 mm and TST-10 mm, correspondingly. These results indicate that 128 (17.6 %), 112 (15.4 %) and 157 (21.6 %) patients with a diagnosis of active TB had a false negative result with IGRA, TST-5 mm and TST-10 mm tests, respectively. Table 1 presents the sensitivity results for IGRA and TST for total of patients and stratified by sociodemographic and clinical variables.

Comparing the sensitivity of the tests separately with the combined sensitivity of IGRA/TST-5 mm and IGRA/TST-10 mm (91.7 % and 90.6 %, respectively), the latter was consistently higher and this difference was statistically significant ($p < 0.001$) – Fig. 1.

Risk factors for IGRA indeterminate results

Of the 161 patients with an indeterminate result, the majority were male (67.7 %) with a mean age of 56.0 (±19.4) that ranged from 5 to 92 years, and more than half were ≥50 years old (57.1 %).

The proportion of indeterminate results increases as the age increases, with patients over 80 years old presenting the highest proportion of indeterminate results (34.5 %) and patients under 20 years old presenting the lowest proportion of indeterminate results (2.9 %).

Being older than 70 years, alcohol abuse and pulmonary TB were independent predictive factors with a statistically significant association to higher probability of indeterminate IGRA results in TB patients (Table 2).

Risk factors for IGRA false negative results

Among the risk factors analyzed through logistic regression (Table 3), two presented a statistically significant association with an increased risk of obtaining false negative IGRA results - inflammatory diseases and pulmonary TB.

Discussion

The objective of this study was to analyse the performance of an IGRA test in patients with active TB which involved establishing and comparing the sensitivity of IGRA and TST tests.

IGRA sensitivity results are heterogeneous across the literature, ranging from 60 %[11] to nearly 100 %[12] with most studies presenting an sensitivity above 70 %, as demonstrated by three different meta-analyzes that obtained a pooled sensitivity of 81.0 %,[13] 80.0 %[14] and 84.2 %.[15] In our study, IGRA overall sensitivity (82.4 %) was close to the pooled sensitivity of these meta-analyzes. Nonetheless, 17.6 % of the results were false negative, demonstrating that although these tests can facilitate diagnostic decisions, negative results should not be used alone to exclude an *M. tuberculosis* infection but interpreted in conjunction with other clinical findings and diagnoses.

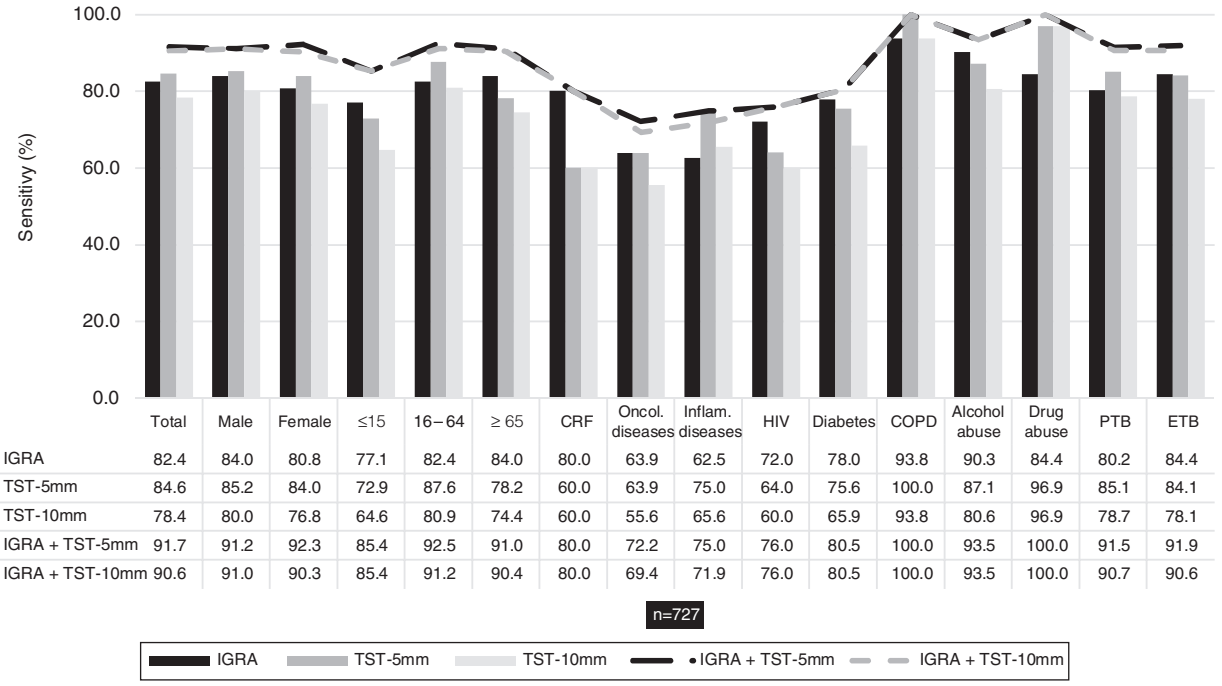
Our TST sensitivity was higher than the pooled sensitivity obtained in three different meta-analysis - 66 %,[15] 70 %[13] and 77 %[16] - but comparable to a US TB surveillance study that included almost 65 000 culture-confirmed TB patients, in which 84.2 % of the patients had a TST≥5 mm and 81.6 % a TST ≥ 10 mm.[17] Despite the differences in sensitivity obtained between IGRA and TST-5 mm or TST-10 mm, only the difference between IGRA and TST-10 mm was statistically significant ($p = 0.021$), which indicates that IGRA and TST-5 mm had an similar performance in the identification of cases of infection and presented a better performance than TST-10 mm.

By combining the results of the two tests, the sensitivity increased to more than 90.0 %, and the difference between these results and those obtained by the tests separately was statistically significant ($p < 0.001$). Choi et al. presented similar sensitivity results, obtaining 85.3 % (TST), 70.3 % (IGRA) and 93.3 % (IGRA/TST).[4] This increase in sensitivity suggests that the combined use of the two tests could promote the identification of more cases of infection than if used sepa-

Table 1 IGRA and TST sensitivity (5 mm and 10 mm cut-offs) according to sex, age group, comorbidities (chronic renal failure, oncologic disease, inflammatory disease, HIV, diabetes and COPD), substance abuse (alcohol or drug abuse) and site of disease (pulmonary or extrapulmonary) in patients submitted to both assays (n = 727).

	Variables	Patients	IGRA		TST - 5 mm		TST - 10 mm	
	n/N (%)	Positive (n)	Sensitivity % (IC 95%)	Positive (n)	Sensitivity % (IC 95%)	Positive (n)	Sensitivity % (IC 95%)	
Total		727	599	82.4 (79.5–84.9)	615	84.6 (82.0–87.2)	570	78.4 (75.4–81.4)
Sex	Male	362/727 (49.8)	304	84.0 (79.9–87.4)	311	85.2 (81.6–88.8)	292	91.2 (88.3–94.1)
	Female	365/727 (50.2)	295	80.8 (76.5–84.5)	304	84.0 (80.2–87.8)	278	92.3 (89.5–95.0)
Age group	≤15	48/727 (6.6)	37	77.1 (63.5–86.7)	35	72.9 (60.3–85.5)	31	85.4 (75.4–95.4)
	16 – 64	523/727 (71.9)	431	82.4 (78.9–85.4)	458	87.6 (84.7–90.4)	423	92.5 (90.3–95.0)
	≥ 65	156/727 (21.5)	131	84.0 (77.4–88.9)	122	78.2 (71.7–84.7)	116	91.0 (86.5–95.5)
Comorbidities	Chronic renal failure	5/727 (0.7)	4	80.0 (37.6–96.4)	3	60.0 (14.7–94.7)	3	80.0 (28.4–99.5)
	Oncologic diseases	36/727 (5.0)	23	63.9 (47.6–77.5)	23	63.9 (48.2–79.6)	20	72.2 (57.6–86.9)
	Inflammatory diseases	32/727 (4.4)	20	62.5 (45.3–77.1)	24	75.0 (60.0–90.0)	21	75.0 (60.0–90.0)
	HIV infection	25/632 (3.4)	18	72.0 (52.4–85.7)	16	64.0 (44.5–79.8)	15	76.0 (56.6–88.5)
	Diabetes	41/727 (5.6)	32	78.0 (63.3–88.0)	31	75.6 (62.5–88.8)	27	80.5 (68.4–92.6)
	COPD	16/727 (2.2)	15	93.8 (71.7–98.9)	16	100 (79.4–100)	15	100 (79.4–100)
Substance abuse	Alcohol abuse	31/706 (4.3)	28	90.3 (75.1–96.7)	27	87.1 (75.3–98.9)	25	93.5 (78.6–99.2)
	Drug abuse	32/709 (4.4)	27	84.4 (68.3–93.1)	31	96.9 (83.8–99.9)	31	100 (89.1–100)
Site of disease	PTB	343/727 (47.2)	275	80.2 (75.6–84.1)	292	85.1 (81.4–88.9)	270	91.5 (88.6–94.5)
	ETB	384/727 (52.8)	324	84.4 (80.4–87.7)	323	84.1 (80.5–87.8)	300	91.9 (89.2–94.7)

PTB = Pulmonary tuberculosis; ETB = Extrapulmonary tuberculosis.



	Total	Male	Female	≤15	16–64	≥65	CRF	Oncol. diseases	Inflam. diseases	HIV	Diabetes	COPD	Alcohol abuse	Drug abuse	PTB	ETB
IGRA	82.4	84.0	80.8	77.1	82.4	84.0	80.0	63.9	62.5	72.0	78.0	93.8	90.3	84.4	80.2	84.4
TST-5mm	84.6	85.2	84.0	72.9	87.6	78.2	60.0	63.9	75.0	64.0	75.6	100.0	87.1	96.9	85.1	84.1
TST-10mm	78.4	80.0	76.8	64.6	80.9	74.4	60.0	55.6	65.6	60.0	65.9	93.8	80.6	96.9	78.7	78.1
IGRA + TST-5mm	91.7	91.2	92.3	85.4	92.5	91.0	80.0	72.2	75.0	76.0	80.5	100.0	93.5	100.0	91.5	91.9
IGRA + TST-10mm	90.6	91.0	90.3	85.4	91.2	90.4	80.0	69.4	71.9	76.0	80.5	100.0	93.5	100.0	90.7	90.6

Figure 1 Sensitivity of IGRA and TST when used separately and when used together (IGRA/TST-5 mm and IGRA/TST-10 mm) in patients with both test results (n = 727). Sensitivity was assessed according to sex, age group (≤15, 16-64, ≥65 years), comorbidities (chronic renal failure [CRF], oncologic disease, inflammatory disease, HIV infection, diabetes and COPD), substance abuse (alcohol or drug abuse) and site of disease (pulmonary TB [PTB] or extrapulmonary TB [ETB]).

rately and in substitution of one another. The combined use could enhance the detection of LTBI cases among vulnerable populations,[18] such as homeless people, drug or alcohol abusers, prisoners and people living with HIV. This approach could be especially helpful in low-incidence countries, as the majority of TB cases occur due to the progression from LTBI to TB disease.[19] Furthermore, these vulnerable populations are frequently associated with individual and contextual factors, as presented by Zão et al,[20] that contribute to patient and healthcare system delay in the diagnosis and treatment of TB. A false negative result could contribute to longer delays, thus perpetuating the spread of the disease.

Indeterminate results represent a considerable problem for clinical management, since they imply the lack of clear information about the patient's TB infection status.

Unlike other studies,[21,22] our results do not show old age as a risk factor for false negative IGRA results. However, we observed that older age was a predictive factor for indeterminate results, which was consistent with the findings of other studies.[21,23] Several studies analyzed the association between age and indeterminate IGRA results and concluded that indeterminate results are significantly more common in children[23–25] and adolescents[23] and in the elderly.[23,26] Our results confirm part of their conclusions, with patients aged >80 years being seven times more likely to have an indeterminate IGRA result. In addition, when we stratified patients in ten-year age groups, we observed that the proportion of indeterminate results increased as the age increases, with patients over 80 years old presenting the highest proportion of indeterminate results, results shared with Kobashi et al.[26] In our study younger patients did not present any association with false negative or indeterminate IGRA results.

Our study also found an association between alcohol abuse and indeterminate IGRA results in which patients with an alcohol problem were four times more likely to have an indeterminate outcome. Both acute and chronic alcohol use have profound regulatory effects on the immune system,[27] which possibly impairs the patient's ability to respond correctly to the IGRA, resulting in an indeterminate result. Because alcohol dependence was based on self-report and daily alcohol intake was not determined, further studies with a more detailed information on alcohol consumption are needed to better understand this potential association.

From the studies available involving IGRA, PTB patients and ETB patients, the test sensitivity remains similar in both forms of TB, as shown by Di et al.[28] (89.7 % vs 79.7 %), Ji et al.[29] (89.7 % vs 87.6 %), Azghay et al.[30] (78.9 % vs 87.8 %) and in our study (80.2 % vs 84.4 %). However, pulmonary TB was presented as a predictive factor for indeterminate and false negative results, in which these patients were almost three times more likely to have an indeterminate outcome and nearly twice as likely to have a false negative result compared to extrapulmonary TB (ETB) patients.

Clinical manifestations of ETB may vary from an acute or disseminated disease, such as meningitis or miliary TB, to a chronic localized infection with an insidious onset and slow progression, such as lymph node or osteoarticular TB.[31,32] In two analyses of risk factors of false-negative IGRA results, only meningitis TB from the eight forms of ETB in one study and 6 forms in the other was significantly associated with false negative results, an acute clinical manifestation.[28,33] Thus, the fact that most ETB manifestations have a slower progression to severe disease, possibly allows patients to maintain a functional immune system and consequently

Table 2 Sociodemographic and clinical characteristics of 161 patients with indeterminate IGRA results and their association with the occurrence of the indeterminate test results in patients with active TB.

	Variables (reference class) n (%)	Indeterminate IGRA	Crude Odds Ratio		Adjusted Odds ratio (by sex and age)		Final Model (FR)	
		OR (95 %CI)	*p*	OR (95 %CI)	*p*	OR (95 %CI)	*P*	
Sex (Female)	Male	109 (67.7)	1.94 (1.37–2.76)	<0.001	1.95 (1.37–2.8)	<0.001		
Age	<10	1 (0.6)	0.23 (0.03–1.75)	0.155	0.23 (0.03–1.79)	0.161		
group	11-20	2 (1.2)	0.24 (0.06–1.05)	0.059	0.23 (0.05–1.01)	0.061		
(41–50)	21-30	12 (7.5)	0.83 (0.40–1.71)	0.616	0.88 (0.43–1.82)	0.735		
	31-40	28 (17.4)	1.36 (0.77–2.40)	0.296	1.41 (0.79–2.49)	0.246		
	51-60	26 (16.1)	1.10 (0.59–2.03)	0.753	1.11 (0.60–2.05)	0.741		
	61-70	21 (13.0)	1.26 (0.63–2.12)	0.639	1.23 (0.67–2.26)	0.508		
	71 - 80	30 (18.6)	1.79 (1.01–3.15)	0.045	1.83 (1.03–3.24)	0.039	2.52 (1.16–5.48)	0.020
	> 80	19 (11.8)	4.24 (2.13–8.45)	<0.001	4.21 (2.1–8.44)	<0.001	7.22 (2.83-18.4)	<0.001
Comorbidities (No)	Chronic renal failure	1 (0.6)	0.51 (0.07–3.91)	0.515	0.34 (0.04–2.76)	0.313		
	Oncologic diseases	13 (8.1)	1.45 (0.78–2.71)	0.241	1.06 (0.55–2.03)	0.873		
	Inflammatory diseases	5 (3.1)	0.67 (0.26–1.70)	0.397	0.63 (0.24–1.64)	0.340		
	HIV infection	14 (8.7)	1.79 (0.97–3.33)	0.061	1.76 (0.91–3.4)	0.092		
	Diabetes	16 (9.9)	1.79 (1.01–3.19)	0.047	1.59 (0.87–2.95)	0.134		
	COPD	9 (5.6)	2.69 (1.22–5.93)	0.014	1.81 (0.79–4.15)	0.159		
Substance abuse	Alcohol abuse	27 (16.8)	4.15 (2.52–6.83)	<0.001	4.07 (2.36–7.01)	<0.001	4.17 (2.23–7.81)	<0.001
(No)	Drug abuse	15 (9.3)	2.52 (1.37–4.64)	0.003	2.75 (1.41–5.35)	0.003		
Site of disease (ETB)	PTB	116 (72.0)/45 (28.0)	3.15 (2.19–4.54)	<0.001	3.544 (2.43–5.18)	<0.001	2.85 (1.79–4.53)	<0.001

OR = Odds ratio; CI = confidence interval; PTB = Pulmonary tuberculosis; ETB = Extrapulmonary tuberculosis. FR - Forward stepwise (LR).

Table 3 Association between false negative IGRA results and sociodemographic and clinical variables among patients with notified TB (n = 1069).

	Variables (reference class) n/N (%)	Patients	Crude Odds Ratio		Adjusted Odds ratio (by sex and age)		Final Model (FR)	
		OR (95 %CI)	*p*	OR (95 %CI)	*p*	OR (95 %CI)	*p*	
Sex (Female)	Male	555/1069 (51.9)	0.87 (0.64–1.17)	0.352	0.86 (0.63–1.16)	0.325		
Age	<10	35/1069 (3.3)	1.34 (0.60–2.99)	0.472	1.34 (0.60–2.98)	0.476		
group	11-20	66/1069 (6.2)	0.75 (0.37–1.51)	0.413	0.75 (0.37–1.52)	0.428		
(41–50)	21-30	116/1069 (10.9)	0.97 (0.56–1.67)	0.909	0.96 (0.55–1.65)	0.872		
	31-40	166/1069 (15.5)	0.83 (0.51–1.37)	0.471	0.82 (0.49–1.36)	0.445		
	51-60	209/1069 (19.6)	0.62 (0.36–1.07)	0.088	0.62 (0.36–1.07)	0.084		
	61-70	153/1069 (14.3)	0.66 (0.38–1.12)	0.122	0.65 (0.38–1.11)	0.111		
	71 - 80	153/1069 (14.3)	0.84 (0.49–1.43)	0.516	0.83 (0.49–1.41)	0.493		
	> 80	135/1069 (12.6)	0.81 (0.33–1.96)	0.64	0.82 (0.34–1.99)	0.66		
Comorbidities (No)	Chronic renal failure	13/1069 (1.2)	0.73 (0.16-3.33)	0.687	0.85 (0.18-3.92)	0.835		
	Oncologic diseases	61/1069 (5.7)	1.611 (0.90–2.88)	0.108	1.64 (0.90–2.97)	0.105		
	Inflammatory diseases	49/1069 (4.6)	2.25 (1.22–4.13)	0.009	2.40 (1.29–4.46)	0.006	2.04 (1.04–4.01)	0.039
	HIV infection	59/931 (5.5)	1.22 (0.66–2.28)	0.528	1.18 (0.62–2.24)	0.62		
	Diabetes	62/1069 (5.8)	0.77 (0.38–1.53)	0.452	0.89 (0.44–1.84)	0.767		
	COPD	23/1069 (2.2)	0.85 (0.29–2.52)	0.767	0.93 (0.31–2.79)	0.892		
Substance abuse	Alcohol abuse	57/1029 (5.3)	0.65 (0.30-1.39)	0.263	0.69 (0.32-1.53)	0.371		
(No)	Drug abuse	47/1042 (4.4)	0.96 (0.46–2.01)	0.904	0.93 (0.43–2.0)	0.85		
Site of disease (ETB)	PTB	481/1069 (45.0)	1.71 (1.26–2.31)	0.001	1.67 (1.22–2.29)	0.001	1.69 (1.22–2.35)	0.002

OR = Odds ratio; CI = confidence interval; PTB = Pulmonary tuberculosis; ETB = Extrapulmonary tuberculosis.

functional T-cells which, when presented with TB antigens, will respond with the production of interferon-γ. Another reason for these results may lie in the severity of pulmonary TB cases. Different studies have shown that severe pulmonary disease can be associated with immune suppression which may lead to reduced interferon-γ production.[34,35] During TB progression, the natural cytokine balance is altered while the bacterial load increases, potentially influencing the performance of IGRA tests resulting in a reduction in *M. tuberculosis* specific immune responses, especially interferon-γ production.[36,37]

Considering the existence of highly heterogeneous clinical manifestations associated to the fact that most forms of ETB do not contribute to the transmission of TB, and also considering that research in ETB and their influence in the immune response is scarce, it is imperative to develop further studies in order to better understand the performance of the test in the different clinical manifestations of TB.

We observed that inflammatory diseases were an independent predictive factor for negative IGRA results in patients with active TB. With the growing use of biologic therapies for inflammatory rheumatic diseases and the increased risk of TB associated[38] with their use, our results show that the use of IGRA alone may not be sufficient to eliminate the possibility of an *M. tuberculosis* infection. In view of the high risk of TB in these patients and the possibility of false negative results, a dual testing strategy of IGRA and TST could be more effective for LTBI diagnosis, as other studies involving patients with inflammatory diseases concluded.[39–41]

In our study, five of the 49 patients with inflammatory diseases presented an indeterminate IGRA result but no significant association was found. Some studies have identified an association,[39,42,43] with the corticosteroids used in the treatment of these diseases being the common predictive factor for indeterminate results. No treatment data was available in our study.

Our study has limitations. T-cell assays like IGRA are susceptible to variability by different factors associated with assay manufacturing, pre-analytical processing or analytical testing.[3] However, despite their importance we were unable to determine the impact of these factors on the IGRA results used in the study. Due to the absence of healthy individuals in our study population, it was not possible to estimate the specificity for both immunologic tests, TST and IGRA. The presence of variables based on patient self-report (e.g. alcohol abuse, drug abuse) may have led to a less accurate estimate of the impact of these variables. The use of active TB patients as a proxy to assess the sensitivity of IGRA and TST has the disadvantage that patients with active TB may present immunosuppression due to the disease itself, thus obtaining a different response than with patients with a latent infection or recent infection.

On the other hand, our analysis of the performance of the IGRA test was comprehensive. It involved a considerable number of patients with different risk factors, which allowed observation of the performance of IGRA in different contexts, contributing to a better understanding of how to use this test in populations with certain risk factors. In addition, the comparison with the other screening method for LTBI available (TST) provided additional information on how these tests can be used in order to enhance the detection of cases of infection.

Conclusion

In our study we identified three factors associated with the occurrence of indetermined IGRA results - age over 70 years, alcohol abuse and pulmonary TB.

Inflammatory diseases and pulmonary TB were independent risk factors for false negative IGRA results in patients with active TB.

Given the impact that treatments of inflammatory diseases have on the development of active TB, our results suggest a careful interpretation of a negative result, since there is a significant risk of false negative results.

The fact that the IGRA appears to perform well in patients with ETB (less indeterminate and false negative results than in patients with pulmonary TB), makes it a valuable diagnostic tool in these cases.

Funding

Fundação para a Ciência e Tecnologia provided financial support to conduct this research [Grant: PTDC/SAU-PUB/31346/2017] but had no involvement in the research itself.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pulmoe.2019.11.001.

References

1. Getahun H, Matteelli A, Abubakar I, Abdel Aziz M, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J. 2015;46(6):1563–76.
2. Matteelli A, Sulis G, Capone S, D'Ambrosio L, Migliori GB, Getahun H. Tuberculosis elimination and the challenge of latent tuberculosis. Press Medicale. 2017;46(2):e13–21.
3. Pai M, Denkinger C, Kik SV, Rangaka M, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014;27(1):3–20.
4. Choi JC, Jarlsberg LG, Grinsdale JA, Osmond DH, Higashi J, Hopewell PC, et al. Reduced sensitivity of the QuantiFERON® test in diabetic patients with smear-negative tuberculosis. Int J Tuberc Lung Dis. 2015;19(5):582–8.
5. Metcalfe JZ, Everett CK, Steingart KR, Cattamanchi A, Huang L, Hopewell PC, et al. Interferon-γ release assays for active pulmonary tuberculosis diagnosis in adults in low-and middle-income countries: Systematic review and meta-analysis. J Infect Dis. 2011;204 SUPPL. 4.
6. Sollai S, Galli L, de Martino M, Chiappini E. Systematic review and meta-analysis on the utility of Interferon-gamma release

assays for the diagnosis of Mycobacterium tuberculosis infection in children: a 2013 update. BMC Infect Dis. 2014;14 Suppl 1(Suppl 1):S6.
7. Mandalakas AM, Detjen AK, Hesseling AC, Benedetti A, Menzies D. Interferon-gamma release assays and childhood tuberculosis: Systematic review and meta-analysis. Int J Tuberc Lung Dis. 2011;15(8):1018–32.
8. Sharninghausen JC, Shapiro AE, Koelle DM, Kim HN. Risk Factors for Indeterminate Outcome on Interferon Gamma Release Assay in Non-US-Born Persons Screened for Latent Tuberculosis Infection. Open Forum Infect Dis. 2018;5(8): 1–8.
9. American Thoracic Society, CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med. 2000;161:221–47.
10. Altman D. Practical statistics for medical research. first edit London: CRC Press; 1991.
11. Dewan PK, Grinsdale J, Kawamura LM. Low Sensitivity of a Whole-Blood Interferon-γ Release Assay for Detection of Active Tuberculosis. Clin Infect Dis. 2007;44(1):69–73.
12. Takasaki J, Manabe T, Morino E, Muto Y, Hashimoto M, Iikura M, et al. Sensitivity and specificity of QuantiFERON-TB Gold Plus compared with QuantiFERON-TB Gold In-Tube and T-SPOT.TB on active tuberculosis in Japan. J Infect Chemother. 2018;24(3):188–92.
13. Diel R, Loddenkemper R, Nienhaus A. Evidence-Based Comparison of Commercial Interferon-γ Release Assays for Detecting Active TB. Chest. 2010;137(April (4)):952–68.
14. Sester M, Sotgiu G, Lange C, Giehl C, Girardi E, Migliori GB, et al. Interferon-γ release assays for the diagnosis of active tuberculosis: A systematic review and meta-analysis. Eur Respir J. 2011;37(1):100–11.
15. Lu P, Chen X, Zhu L, Yang H. Interferon-gamma release assays for the diagnosis of tuberculosis: a systematic review and meta-analysis. Lung. 2016;194(June 2 (3)):447–58.
16. Pai M, Zwerling A, Menzies D. Systematic Review : T-Cell – based Assays for the Diagnosis of Latent Tuberculosis Infection : An Update. Ann Intern Med. 2008;149:177–84.
17. Auld SC, Click ES, Heilig CM, Miramontes R, Cain KP, Bisson GP, et al. Association Between Tuberculin Skin Test Result and Clinical Presentation of Tuberculosis Disease. BMC Infect Dis. 2013;13:460.
18. Heuvelings CC, Vries SG, Grobusch MP. Tackling TB in low-incidence countries: improving diagnosis and management in vulnerable populations. Int J Infect Dis. 2017;56(March):77–80.
19. Blumberg HM, Ernst JD. The Challenge of Latent TB Infection. JAMA. 2016;316(September 6 (9)):931.
20. Zão I, Ribeiro AI, Apolinário D, Duarte R. Why does it take so long? The reasons behind tuberculosis treatment delay in Portugal. Pulmonology. 2019;25(4):215–22.
21. Cho K, Cho E, Kwon S, Im S, Sohn I, Song S, et al. Factors Associated with Indeterminate and False Negative Results of QuantiFERON-TB Gold In-Tube Test in Active Tuberculosis. Tuberc Respir Dis (Seoul). 2012;72(5):416.
22. Kwon Y-S, Kim YH, Jeon K, Jeong B-H, Ryu YJ, Choi JC, et al. Factors that Predict Negative Results of QuantiFERON-TB Gold In-Tube Test in Patients with Culture-Confirmed Tuberculosis: A Multicenter Retrospective Cohort Study. PLoS One. 2015;10(6):e0129792.
23. Tebruegge M, De Graaf H, Sukhtankar P, Elkington P, Marshall B, Schuster H, et al. Extremes of age are associated with indeterminate QuantiFERON-TB gold assay results. J Clin Microbiol. 2014;52(7):2694–7.
24. Bergamini BM, Losi M, Vaienti F, D'Amico R, Meccugni B, Meacci M, et al. Performance of Commercial Blood Tests for the Diagnosis of Latent Tuberculosis Infection in Children and Adolescents. Pediatrics. 2009;123(March 1 (3)): e419–24.
25. Rose MV, Kimaro G, Nissen TN, Kroidl I, Hoelscher M, Bygbjerg IC, et al. Quantiferon®-TB gold in-tube performance for diagnosing active tuberculosis in children and adults in a high burden setting. PLoS One. 2012;7(7):1–10.
26. Kobashi Y, Sugiu T, Mouri K, Obase Y, Miyashita N, Oka M. Indeterminate results of QuantiFERON TB-2G test performed in routine clinical practice. Eur Respir J. 2009;33(4):812–5.
27. Friedman H, Pross S, Klein TW. Addictive drugs and their relationship with infectious diseases. FEMS Immunol Med Microbiol. 2006;47(3):330–42.
28. Di L, Li Y. The risk factor of false-negative and false-positive for T-SPOT.TB in active tuberculosis. J Clin Lab Anal. 2018; 32(2).
29. Ji L, Lou YL, Wu ZX, Jiang JQ, Fan XL, Wang LF, et al. Usefulness of interferon-γ release assay for the diagnosis of sputum smear-negative pulmonary and extra-pulmonary TB in Zhejiang Province. China. Infect Dis Poverty. 2017;6(1): 1–5.
30. Azghay M, Bouchaud O, Mechai F, Nicaise P, Fain O, Stirnemann J. Utility of QuantiFERON-TB Gold In-Tube assay in adult, pulmonary and extrapulmonary, active tuberculosis diagnosis. Int J Infect Dis. 2016;44:25–30.
31. Houston A, Macallan DC. Extrapulmonary tuberculosis. Medicine (Baltimore). 2014;42(January (1)):18–22.
32. Sanches I, Carvalho A, Duarte R. Who are the patients with extrapulmonary tuberculosis? Rev Port Pneumol. 2015;21(2):90–3.
33. Kim YJ, Kang JY, Kim S Il, Chang MS, Kim YR, Park YJ. Predictors for false-negative QuantiFERON-TB Gold assay results in patients with extrapulmonary tuberculosis. BMC Infect Dis. 2018;18(1):457.
34. Shams H, Wizel B, Weis SE, Samten B, Barnes PF. Contribution of CD8(+) T cells to gamma interferon production in human tuberculosis. Infect Immun. 2001;69(May (5)): 3497–501.
35. Sodhi A, Gong J, Silva C, Qian D, Barnes PF. Clinical Correlates of Interferon Production in Patients with Tuberculosis. Clin Infect Dis. 1997;25(3):617–20.
36. Vanham G, Toossi Z, Hirsch CS, Wallis RS, Schwander SK, Rich EA, et al. Examining a paradox in the pathogenesis of human pulmonary tuberculosis: Immune activation and suppression/anergy. Tuber Lung Dis. 1997;78(3–4): 145–58.
37. de Visser V, Sotgiu G, Lange C, Aabye MG, Bakker M, Bartalesi F, et al. False-negative interferon-γ release assay results in active tuberculosis: a TBNET study. Eur Respir J. 2015;45(January (1)):279–83.
38. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2010;69(March (3)): 522–8.
39. Vassilopoulos D, Tsikrika S, Hatzara C, Podia V, Kandili A, Stamoulis N, et al. Comparison of two gamma interferon release assays and tuberculin skin testing for tuberculosis screening in a cohort of patients with rheumatic diseases starting anti-tumor necrosis factor therapy. Clin Vaccine Immunol. 2011;18(12):2102–8.
40. So H, Yuen CS, Yip RM. Comparison of a commercial interferon-gamma release assay and tuberculin skin test for the detection of latent tuberculosis infection in Hong Kong arthritis patients who are candidates for biologic agents. Hong Kong Med J. 2017:1–5.
41. Song G, Bae S, Lee Y. Interferon-gamma release assays versus tuberculin skin testing in patients with rheumatoid arthritis (Provisional abstract). Int J Rheum Dis. 2013;16: 279–83.

42. Cho H, Kim YW, Suh C-H, Jung J-Y, Um Y-J, Jung J-H, et al. Concordance between the tuberculin skin test and interferon gamma release assay (IGRA) for diagnosing latent tuberculosis infection in patients with systemic lupus erythematosus and patient characteristics associated with an indeterminate IGRA. Lupus. 2016;25(Oct 11 (12)):1341–8.

43. Kaur M, Singapura P, Kalakota N, Cruz G, Shukla R, Ahsan S, et al. Factors That Contribute to Indeterminate Results From the QuantiFERON-TB Gold In-Tube Test in Patients With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2018;16(10), 1616-1621.e1.

Pulmonol. 2020;**26(6)**:363–369

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

The addition of a humidifier device to a circuit and its impact on home ventilator performance: a bench study

Javier Collada-Carrasco[a,*], Cristina Lamolda-Puyol[b], Manel Luján[b], Alba Castaño-Menéndez[a], Miguel Jiménez-Gómez[a], Ana Hernández-Voth[a], Javier Sayas-Catalán[a]

[a] *Hospital Universitario Doce De Octubre, Madrid, Spain*
[b] *Hospital Parc Taulí De Sabadell, Barcelona, Spain*

Received 26 July 2019; accepted 1 November 2019
Available online 26 December 2019

KEYWORDS
Non-invasive ventilation;
Humidifiers;
Proof of concept study;
Airflow obstruction

Abstract
Introduction and objectives: Humidification and non-invasive ventilation are frequently used together, despite the lack of precise recommendations regarding this practice. We aimed to analyse the impact of active external and built-in humidifiers on the performance of home ventilators, focusing on their pressurization efficacy and their behaviour under different inspiratory efforts.
Methods: We designed a bench study of a lung simulator programmed to emulate mechanical conditions similar to those experienced by real respiratory patients and to simulate three different levels of inspiratory effort: five different commonly used home NIV devices and active humidifiers attached to the latter (internal or ''built-in'') or to the circuit (external). To test ventilator pressurization under different humidification and effort settings, pressure-time products in the first 300 ms and 500 ms of the respiratory cycle were calculated in the 45 situations simulated. Inferential statistical analysis was performed.
Results: A significant reduction of PTP 300 and PTP 500 was observed with the external humidifier in three of the devices. The same pattern was noted for another device with an internal humidifier, and only one device showed no significant changes. This impact on pressurization was commonly higher under high inspiratory effort.

Abbreviations: NIV, non-invasive ventilation; PTP, pressure-time product; HI, internal humidifier; HE, external humidifier; IE, inspiration:expiration; TV, tidal volume; P/T, pressure/time; PPlat, pressure-plateau; NS, non-significant; ADC, analogue to digital converter.

* Corresponding author at: Hospital Universitario Doce de Octubre, Avda. de Córdoba S/N. 28041, Madrid, Spain.
E-mail addresses: javiercollada91@gmail.com, javier.collada@salud.madrid.org (J. Collada-Carrasco), clalmolda@tauli.cat (C. Lamolda-Puyol), mlujan@tauli.cat (M. Luján), albacm1991@gmail.com (A. Castaño-Menéndez), migueljimenezgomez@gmail.com (M. Jiménez-Gómez), anahvoth@gmail.com (A. Hernández-Voth), jsayascat@gmail.com (J. Sayas-Catalán).

https://doi.org/10.1016/j.pulmoe.2019.11.004

Conclusions: These results indicate the need to monitor pressure changes in the use of external humidification devices in some home NIV ventilators.

Introduction

Data on the efficacy of non-invasive mechanical ventilation (NIV) in improving breathlessness, arterial blood gases and respiratory drive and its usefulness in preventing the need for intubation in many cases is currently undeniable.[1] A large number of patients benefit from this therapy during our daily clinical practice. Despite the absence of high-quality evidence on its use and efficacy, humidification during therapy with NIV is widespread, both in the acute care setting and in home care.

The need for air humidification is widely accepted in invasive mechanical ventilation to prevent harmful effects on respiratory airways and to preserve normal respiratory function.[2] However, the importance of this measure has been traditionally overlooked in NIV, which has been considered to respect the physiological humidification of air in the upper airways. However, physiological conditioning of air could become insufficient with NIV, as the air delivered by the ventilator is colder and dryer than ambient air, as a result of the common presence of leaks in the NIV circuit and the high unidirectional flow by which this air is delivered.[3] Although upper airways are not bypassed during NIV, high flow from turbine-driven ventilators can make physiological humidification less effective.

Active humidification devices are preferred in NIV.[7] There are two types available for home care ventilators: internal humidifiers (HI; built into the ventilator) and external humidifiers (HE; often connected to the ventilator by passive, unheated tubing). Humidifiers could be beneficial in reducing airflow resistance and patient discomfort and intolerance,[4,5] usually linked to NIV failure. Even when NIV fails, humidification turns out to be useful in some studies in facilitating patient intubation when indicated.[6] However, only recent studies have examined the effect of using different types of hospital care humidifiers, heaters and tubing on the performance of ventilators regarding pressurization.[8] To date, no studies have examined this effect on home care ventilators.

The aim of the present study was to assess the effect on ventilator pressurization performance of adding an external or internal (built-in) humidifier to the patient-ventilator circuit.

Material and methods

We conducted an experimental bench study connecting 5 NIV devices commonly employed in home non-invasive ventilation to a lung simulator. The effect on pressurization performance was calculated using the pressure-time product in the first 300 and 500 ms under three different clinical conditions with regard to inspiratory effort (no effort-controlled breaths, medium effort and high effort). We evaluated the performance of the ventilator regarding humidification in three different situations: no humidification (ambient air, no humidifier device attached), external humidifier (HE) and internal (built-in) humidifier (HI).

Simulation model

A lung simulator device (*QuickLung® + Breather®, Ingmar Medical, Pittsburgh, PA United States*) was used for all tests. This device is based on a pneumatic balloon, and it can emulate a wide range of different lung compliance and airway resistance values, also allowing us to set the required respiratory rate, inspiration:expiration (I:E) ratio and spontaneous tidal volume (TV).

Previous studies[9] have established the relationship between the level of patient inspiratory effort and the variable P 0.1, defined as the airway pressure generated over 100 ms by the inspiratory effort. Thus, a P 0.1 value of −4 cmH2O is correlated with medium inspiratory effort, and a P 0.1 value of −8 cmH2O is correlated with high inspiratory effort. Taking this into account, we set the simulator device to the required tidal volume to achieve these P 0.1 values, emulating the aforementioned three different scenarios: no effort (controlled ventilation), medium effort (assisted ventilation, simulator tidal volume 350 mL) and high effort (assisted ventilation, simulator tidal volume 610 mL).

A pre-defined compliance value of 50 mL/cmH2O and an airway resistance value of 20 cmH2O/L/s was set in the model to simulate a patient with a severe obstructive ventilator disease, as these obstructive patients may be more prone to flow demand and under-assistance when low pressurization rates are employed. We set a spontaneous respiratory rate of 15 bpm, with an I:E ratio of 0.45.

Standard 22-mm diameter and 160-cm length (*Model 5805000, Intersurgical®, Berkshire, United Kingdom*) tubing was employed to connect the simulator device with each evaluated ventilator. We attached a standard, calibrated passive leak port to the circuit, proximal to the simulator (*Whisper Swivel®, Philips Respironics, Murrysville, PA United States*), similar to others commonly used in hospital NIV (Fig. 1).

Measurement of variables

The flow delivered by each ventilator was measured by a calibrated pneumotachograph (*MLT1000L®, Ad Instruments, New South Wales, Australia*) located close to the simulator

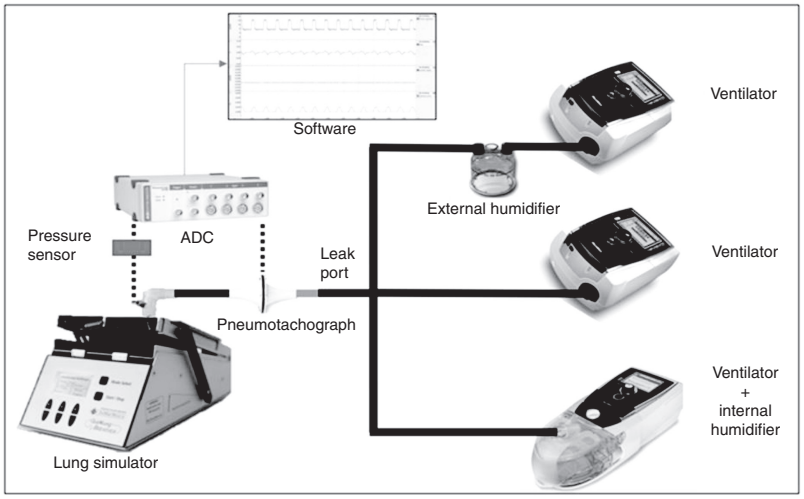


Figure 1 Simplified scheme of model composition. Every ventilator was connected by means of standard tubing to the lung simulator. Data measured by interposed pneumotachograph and pressure sensor were converted and analysed by specific software. ADC: Analogue to digital converter.

inlet distal to the intentional leak. The signal was acquired, filtered and processed through a differential pressure sensor (*SpirometryPod®, Ad Instruments, New South Wales, Australia*). The pressure was measured by a high-precision sensor, and the signal was conditioned and filtered with a pressure transducer (*MLT380® and BridgePod®, Ad Instruments, New South Wales, Australia*).

Both flow and pressure signals were digitalized at an acquisition rate of 200 Hz with an analogue to digital converter (*PowerLab® 26 T, Ad Instruments, New South Wales, Australia*), and data were subsequently analysed with dedicated software (*LabChart® 8 and Peak Analysis, Ad Instruments, New South Wales, Australia*) (Fig. 1).

Study protocol

We tested five different home NIV devices commonly employed in our NIV unit and easily available in the EU. All of them were suitable for the use of an internal (built-in) humidifier and an external humidifier:

Ventilator 1: Vivo®40, Breas Medical, Mölnlycke, Sweden.

Ventilator 2: Stellar®150, ResMed, San Diego, CA United States.

Ventilator 3: VPAP S9®, ResMed, San Diego, CA United States.

Ventilator 4: DreamStation®, Philips Respironics, Murrysville, PA United States.

Ventilator 5: Lumis®150, ResMed, San Diego, CA United States.

Each ventilator was programmed with common pre-set parameters: 1. IPAP 15 cmH2O, EPAP 4 cmH2O; 2. Backup respiratory rate 5 bpm; 3. Rise time value as low as allowed by each device; 4. Inspiratory trigger as sensitive as possible without auto-triggering; and 5. Expiratory trigger 50 % of peak inspiratory flow (in this case, ventilator 4 was programmed Autotrak mode). The maximum inspiratory time, when adjustable, was set as high as possible to avoid time-cycling. In devices 1 and 4, a pre-set inspiratory time of 1.2 s was set for controlled breaths. Whenever a circuit recognition option was present (ventilators 2 and 4), circuit recognition was performed before each test.

Each ventilator was tested in three different scenarios according to humidifiers: no humidification, external humidifier (HE) and internal ''built-in'' humidifier (HI) (Fig. 1). The external humidifier employed was an HC500® (*Fisher&Paykel®, East Tamaki, New Zealand*), commonly recommended by manufacturers. We used room-temperature water (approximately 25 °C) to avoid differences in air temperature and density, which could add extra variability to our measurements. All tests were performed the same day within a time frame of 4 h and in room air with no added oxygen. A small 22-mm tube connected the humidifier chamber to the ventilator when the HE was used (*24-inch gray* 1006833 *REMstar® humidifier tubing, Philips Respironics, Murrysville, PA, United States*)

In this model, the total circuit air volume (so-called *compliant volume*) resulting after the addition of the humidifier was considerably higher with HE (350 mL) than with HI (200 mL); both were always filled to the maximum recommended level to reduce compliant volume as much as possible.

With respect to the ventilators, three different humidifier situations and three different efforts were tested, so each ventilator was tested in 9 different model configurations.

Two minutes of digital flow/time and pressure/time (P/T) curves were recorded in each situation, and data from five consecutive representative respiratory cycles (specifically, data concerning five consecutive P/T curves) were selected for analysis in each case. The analysis was carried out using the *Peak Analysis* tool (*LabChart® 8*), obtaining the median area under the P/T curve (AUC) value, both in the first 300 ms and in the first 500 ms of each cycle. These values of PTP300 (cmH2O $\times$ ms) and PTP500 (cmH2O $\times$ ms) reflect the pressurization rate of the ventilator during the initial phase (PTP300) and during the pressure maintenance phase (PTP500).[10]

	MEDIAN PTP 300 [Q3-Q1]	MEDIAN PTP 500 [Q3-Q1]
VENTILATOR 1 (*Vivo®40*)		
BASAL	2,157 [2,171-1,842]	4,387 [4,428-4,027]
HE	2,073 [2,121-1,791]	4,317 [4,334-3,946]
p value	< 0,05*	< 0,05*
HI	2,092 [2,131-1,785]	4,297 [4,391-3,933]
p value	NS	NS
VENTILATOR 2 (*Stellar®150*)		
BASAL	1,948 [1,979-1,714]	4,227 [4,293-3,962]
HE	1,942 [1,975-1,682]	4,19 [4,246-3,877]
p value	NS	NS
HI	1,908 [1,940-1,653]	4,132 [4,203-3,833]
p value	< 0,05*	< 0,05*
VENTILATOR 3 (*VPAP S9®*)		
BASAL	1,761 [1,774-1,654]	4,02 [4,036-3,874]
HE	1,755 [1,760-1,590]	3,94 [3,953-3,737]
p value	0,05	< 0,05*
HI	1,776 [1,794-1,624]	4,042 [4,073-3,842]
p value	NS	NS
VENTILATOR 4 (*DreamStation®*)		
BASAL	1,921 [2,049-1,91]	3,864 [4,011-3,817]
HE	1,862 [2,004-1,851]	3,762 [3,943-3,704]
p value	< 0,01**	< 0,05*
HI	1,919 [2,054-1,895]	3,863 [4,034-3,790]
p value	NS	NS
VENTILATOR 5 (*Lumis®150*)		
BASAL	1,786 [1,868-1,616]	4,082 [4,192-3,903]
HE	1,772 [1,837-1,575]	4,013 [4,108-3,791]
p value	NS	NS
HI	1,798 [1,875-1,605]	4,089 [4,196-3,876]
p value	NS	NS

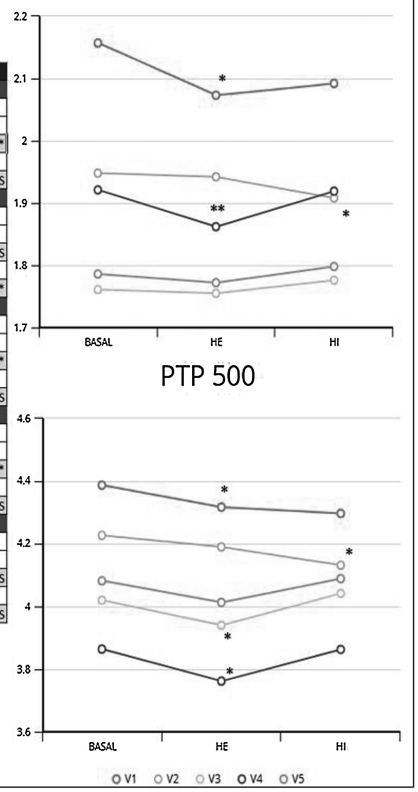


Figure 2 Comparative representation of median PTP300 and PTP500 according to NIV device and type of humidification. HE: external humidifier; HI: internal humidifier; V1: Vivo®40; V2: Stellar®; V3: VPAP S9®; V4: DreamST®; V5: Lumis® 150; *: $p < 0.05$; **$p < 0.01$. NS: non-significant.

Statistical analysis

We employed *SPSS® Statistics v.22* (*IBM®, Armonk, NY United States*) software for data analysis. Outcome variables (PTP300 and PTP500) were tested for normality with the *Kolmogorov-Smirnov* and *Shapiro-Wilk* normality tests. We used the Mann-Whitney *U* test to contrast the value of PTP300 and PTP500 when each ventilator was connected to HE and HI with its value without a humidification device. The results were considered significant with a p value <0.05.

We performed linear univariate analysis describing the influence of each factor (NIV device, humidification, inspiratory effort) or the distinct combination of factors over the value of PTP300 and PTP500. We considered the F value to be significant when the p value was < 0.05.

Results

A significant reduction of PTP300 and PTP500 was found with the use of HE compared with no humidifier in ventilators 1 and 4, and ventilator 3 exhibited a reduction only in PTP500.

In addition, a significant reduction of PTP300 and PTP500 was observed in ventilator 2 with the use of an HI and was not found with an external humidifier.

Ventilator 5 was the only one that could to maintain PTP300 and PTP500, despite the use of different humidifiers and within diverse effort scenarios (Fig. 2).

Both the ventilator model and the type of humidification were shown to significantly influence the values of PTP300 and PTP500, up to 46 % and 41 %, respectively (PTP300: $F = 17.7$, $p < 0.01$, $R^2 = 0.46$; PTP500: $F = 36.3$, $p < 0.01$, $R^2 = 0.41$). When the degree of inspiratory effort was included, the results were also significant, to the point of increasing the influence over PTP300 and PTP500 to 98 % when the three factors were interacting ($F = 2.597$ and $F = 2.218$, respectively; $p < 0.01$ and $R^2 = 0.98$ in both cases) (Fig. 3).

A further analysis of the influence of inspiratory effort on each ventilator and humidification scenario was performed. Both PTP300 and PTP500 increased their values with medium and high degrees of effort. Whenever a PTP300 and PTP500 drop occurred with the addition of a humidifier, higher effort led to a greater drop in both variables (Fig. 3).

The negative influence of HE on the pressurization rate of ventilators 1 and 4 was significantly greater with high effort (Mann-Whitney *U* test, $p < 0.01$) (Fig. 4). Similarly, ventilator 3 showed a drop in PTP500 with HE through different levels of effort. In contrast, the addition of HI did not influence PTP300 in these devices regardless of the varying levels of effort (Fig. 4). Ventilator 5 maintained pressurization with any humidifier and effort setting. In contrast to others, ventilator 2 displayed a pressurization drop with its specific HI through all inspiratory effort scenarios (Mann-Whitney *U* test, $p < 0.01$).

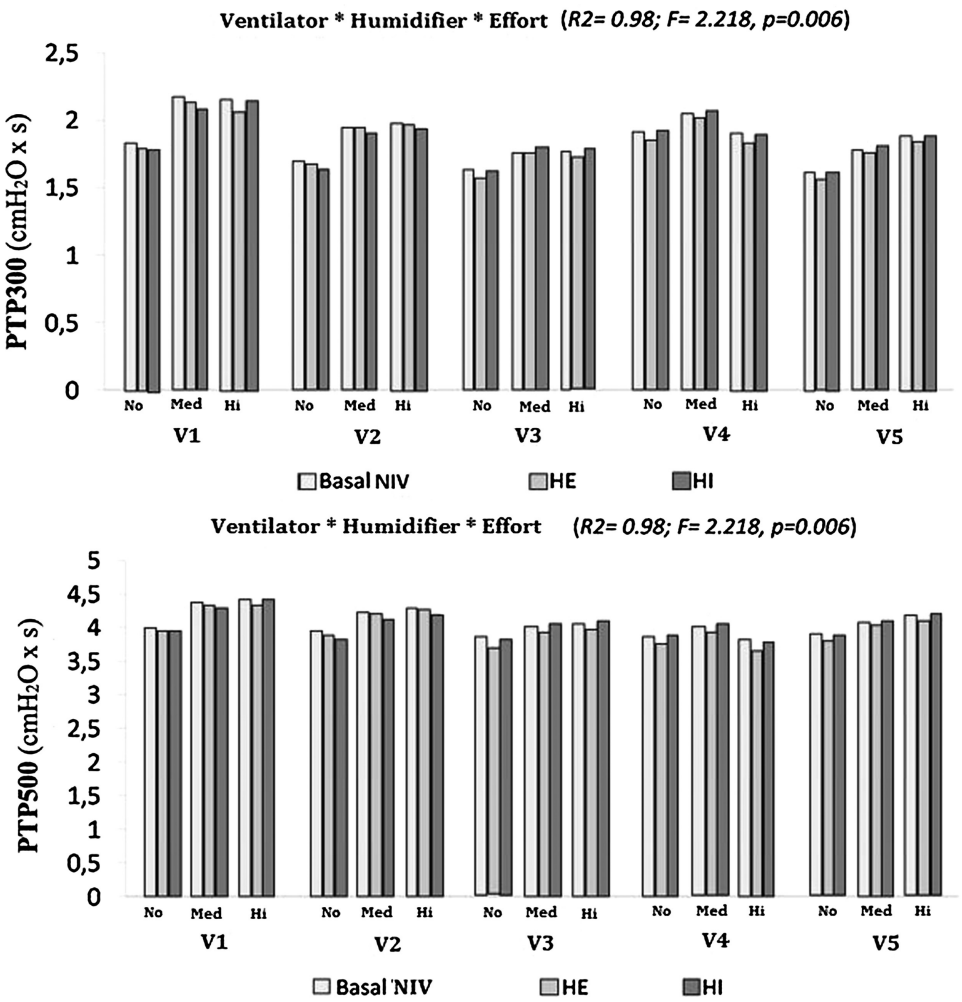


Figure 3 Diagram showing the whole PTP300 and PTP500 range in our study based on ventilator, humidification and inspiratory effort.
HE: external humidifier; HI: internal humidifier; Med: medium effort; Hi: high effort.
V1: Vivo®40; V2: Stellar®; V3: VPAP S9®; V4: DreamST®; V5: Lumis® 150.

VENTILATOR 4 *(DreamStation®)*			
PTP 300 (cmH2O x s)			
	NO EFFORT	MEDIUM EFFORT	HIGH EFFORT
BASAL	1,921	2,053	1,909
HE	1,862	2,012	1,832
p value	< 0,01**	< 0,05*	< 0,01**
HI	1,919	2,063	1,893
p value	NS	NS	NS
PTP 500 (cmH2O x s)			
	NO EFFORT	MEDIUM EFFORT	HIGH EFFORT
BASAL	3,864	4,02	3,815
HE	3,762	3,947	3,665
p value	< 0,05*	< 0,05*	< 0,01**
HI	3,863	4,043	3,79
p value	NS	NS	NS

Figure 4 Detailed representation of the value of PTP300 and PTP500 when different humidification and inspiratory effort situations are combined, in the particular case of ventilator 4.
BASAL: No humidifier; HE: external humidifier; HI: internal humidifier; NS: non-significant.

Discussion

In the present study, three out of five NIV ventilators displayed a negative impact on pressurization when an external humidifier was employed. This effect was attenuated with the use of a built-in humidifier. This can be explained by the increase in circuit compliant volume due to the addition of humidifiers.

The results were remarkably variable on different ventilators. Presumably, ventilators with the best performance on HI were the ones designed by the manufacturer to implement changes in turbine behaviour when their humidifier was detected (i.e., ventilator 5).

A unique case of worse performance with HI was shown on ventilator 2. According to the information provided by the manufacturer, no changes in turbine behaviour are made in this case when the humidifier is plugged. This humidifier chamber is derived from an older model (*VPAP IV®, ResMed, San Diego, CA United States*) and is not advisable for use in acute care settings or for invasive ventilation with the built-in humidifier attached.

Similar results were observed in the recent publication by Alonso-Iñigo and co-workers,[8] which demonstrate that results on ventilatory measurements (i.e., peak inspiratory pressure and flow, Pplat or tidal volume) show significant variation with distinct single-limb heated wire circuits available for clinical use, in spite of ventilator settings and leak compensation algorithms. The explanation they provide for their results relies on the distinct volume, resistance and turbulent flow generated by the circuits.

The reduction of pressurization efficacy observed in several cases with humidifiers seems to be, according to our results, of larger magnitude with high inspiratory effort. This situation may be more relevant to acute or acute-on-chronic respiratory failure when patient respiratory drive is especially high and vigorous inspiratory effort is exerted. Lellouche et al.[11] demonstrated how adding a heat and moisture exchange (HME) filter can increase the work of breathing over a heated humidifier chamber, but no comparison was made regarding their impact over NIV alone in a dedicated turbine ventilator.

In contrast, but equally relevant, chronic NIV setting frequently requires the use of humidifiers, as they are meant to improve day-to-day tolerance. Their utilization is wide, and changes in the ventilator model, humidifier chamber and circuit elements are frequent, with greater or lesser knowledge by the attending physician. This type of modification can distort patient-ventilator synchrony in patients already adapted to the ventilator, potentially modifying the tolerance and efficacy of this therapy in the long-term setting.

Non-invasive ventilation success or failure is determined by many elements, such as the cause and severity of respiratory failure, the neurological or haemodynamic state or, relating to NIV, patient tolerance and patient-ventilator synchrony.[8,12,13] The latter is in turn influenced by, among other factors, ventilator pressurization efficacy.

There are some limitations concerning our study. First, the NIV devices analysed were limited to our more frequently used models. Newer devices have improved airway circuit resistance/compliance detection, thus minimizing these effects.

Second, as we previously explained and to avoid additional confounding factors, we performed our measurements using room-temperature water, although the heating function of humidifiers is frequently used in clinical practice.

Another limitation was the absence of a test on restrictive pulmonary defects. With a restrictive disease (i.e., neuromuscular disease or kyphoscoliosis), the patient might not have as high of a drive as those suffering an obstructive disease, and the influence of the humidifier might be less significant in this setting. Previous studies have suggested that patients with obstructive defects could be more prone to asynchrony than patients with restrictive defects.[14] Moreover, high resistance in the obstructive airways entails a greater challenge for turbine pressurization, and it was our intention to examine the worst-case scenario to prove our hypothesis.

Finally, even though the simulated mechanical conditions could be similar to those of real patients with obstructive ventilatory defects, our study was performed in a controlled and artificial environment. Thus, the results are restricted to the field of simulation and must be interpreted cautiously. Live studies on patients in clinical practice are needed to provide a contrast to these results.

In conclusion, when a humidifier is used with home NIV devices, careful monitoring of possible pressure drops leading to under-assistance should be performed, especially in the acute setting or for end-stage respiratory patients.[15] It is advisable for manufacturers to improve pressurization adjustments when built-in humidifiers are attached to ventilators.

Ethical disclosures

The authors claim that this publication did not involve the use of human subjects and did not imply animal experiments either. The assessment and recommendations made by local ethical committee were taken into account. Since our study was based on a simulation model, use of informed consent was not necessary for its realization.

Conflicts of interest

Manel Luján declares speaking fees from ResMed® and Philips Respironics®, being an active member of the Breas® Clinical Advisory Board.

Javier Sayas-Catalán declares fees from lectures and teaching activities from ResMed®, Philips Respironics® and Chiesi®.

Ana Hernández-Voth declares fees from Chiesi®.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Simonds AK. Home mechanical ventilation: an overview. Ann Am Thorac Soc. 2016;13:2035–44 http://10.0.5.233/AnnalsATS.201606-454FR

2. Tucci MR, Costa EL. Humidification during invasive mechanical ventilation: less lung inflammation with optimal gas conditioning. Resp Care. 2015;60:1854–5, http://dx.doi.org/10.4187/respcare.04512.
3. Tuggey JM, DelMastro M, Elliott MW. The effect of mouth leak and humidification during nasal non-invasive ventilation. Respir Med. 2007;101(9):1874–9, http://dx.doi.org/10.1016/j.rmed.2007.05.005.
4. Branson RD, Gentile MA. Is humidification always necessary during non-invasive ventilation in the hospital? Resp Care. 2010;55:209–16.
5. Lellouche F, Maggiore SM, Lyazidi A, Deye N, Taillé S, Brochard L. Water content of delivered gases during noninvasive ventilation in healthy subjects. Intensive Care Med. 2009;35(6):987–95, http://dx.doi.org/10.1007/s00134-009-1455-y.
6. Esquinas A, Nava S, Scala R, Carrillo A, González G. Humidification and difficult endotracheal intubation in failure of noninvasive mechanical ventilation (NIMV). Am J Respir Crit Care Med. 2008;177:A644.
7. Nava S, Cirio S, Fanfulla F, Carlucci A, Navarra A, Negri A, et al. Comparison of two humidification systems for long-term noninvasive mechanical ventilation. Eur Respir J. 2008;32:460–4, http://dx.doi.org/10.1183/09031936.00000208.
8. Alonso-Iñigo JM, Fas MJ, Abert A, Dolz A, Carratalá JM, Lobato SD. Effects on humidification and ventilatory parameters of three single-limb heated-wired circuits for noninvasive ventilation: a bench study. Arch Bronconeumol. 2019, http://dx.doi.org/10.1016/j.arbres.2019.04.011.
9. Koyama Y, Uchiyama A, Yoshida J, Yoshida T, Yamashita T, Fujino Y. A comparison of the adjustable ranges of inspiratory pressurization during pressure controlled continuous mandatory ventilation of 5 ICU ventilators. Resp Care. 2018;63:936–40, http://dx.doi.org/10.4187/respcare.05286.
10. Jaber S, Tassaux D, Sebbane M, Pouzeratte Y, Battisti A, Capdevila X, et al. Performance characteristics of five new anesthesia ventilators and four intensive care ventilators in pressure-support mode: a comparative bench study. Anesthesiology. 2006;105:944–52, http://dx.doi.org/10.1097/00000542-200611000-00015.
11. Lellouche F, Maggiore SM, Deye N, Taillé S, Pigeot J, Harf A, et al. Effect of the humidification device on the work of breathing during noninvasive ventilation. Intensive Care Med. 2002;28(11):1582–9, http://dx.doi.org/10.1007/s00134-002-1518-9.
12. Garofalo E, Bruni A, Pelaia C, Liparota L, Lombardo N, Longhini F, et al. Recognizing, quantifying and managing patient-ventilator asynchrony in invasive and noninvasive ventilation. Expert Rev. Respir. Med. 2018;12:557–67, http://dx.doi.org/10.1080/17476348.2018.1480941.
13. Lellouche F, Pignataro C, Maggiore SM, Girou E, Deye N, Taillé S, et al. Short-term effects of humidification devices on respiratory pattern and arterial blood gases during noninvasive ventilation. Respir Care. 2012;57:1879–86, http://dx.doi.org/10.4187/respcare.01278.
14. Oto J, Chenelle CT, Marchese AD, Kacmarek RM. A comparison of leak compensation during pediatric noninvasive ventilation: a lung model study. Respir Care. 2014;59(2):241–51, http://dx.doi.org/10.4187/respcare.02616.
15. González-Bermejo J, Janssens P, Rabec C, Perrin C, Lofaso F, Langevin B, et al. SOMNONIV Group. Framework for patient-ventilator asynchrony during long-term non-invasive ventilation. Thorax. 2019;0:1–3, http://dx.doi.org/10.1136/thoraxjnl-2018-213022.

Pulmonol. 2020;**26(6)**:370–377

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Effectiveness of different treatments in obesity hypoventilation syndrome

V.R. Ramírez Molina[a], J.F. Masa Jiménez[b,c,*], F.J. Gómez de Terreros Caro[b], J. Corral Peñafiel[b]

[a] *Pulmonary and Sleep Medicine, Regional General Hospital N.2 of the Mexican Social Security Institute (IMSS), Querétaro, Mexico*
[b] *Division of Pulmonary Medicine, San Pedro de Alcántara Hospital, Cáceres, Spain*
[c] *CIBER of Respiratory Diseases (CIBERES), Madrid, Spain*

Received 14 May 2020; accepted 15 May 2020

KEYWORDS
Obesity;
Hypoventilation;
Sleep apnea;
CPAP;
Positive airway therapy

Abstract Obesity hypoventilation syndrome (OHS) is an undesirable consequence of obesity, defined as daytime hypoventilation, sleep disorder breathing and obesity; during the past few years the prevalence of extreme obesity has markedly increased worldwide consequently increasing the prevalence of OHS. Patients with OHS have a lower quality of life and a higher risk of unfavourable cardiometabolic consequences. Early diagnosis and effective treatment can lead to significant improvement in patient outcomes; therefore, such data has noticeably raised interest in the management and treatment of this sleep disorder. This paper will discuss the findings on the main current treatment modalities OHS will be discussed.

Introduction

Obesity hypoventilation syndrome (OHS) is a disorder characterised by obesity (BMI (body mass index) > 30), daytime hypercapnia and sleep-disordered breathing including severe or moderate obstructive sleep apnea (OSA), combined OSA and hypoventilation, or isolated OHS; after excluding other etiologies of hypoventilation.[1] See Table 1. Around 90% of patients with OHS have related obstructive sleep apnea (OSA)[2] with 73% having severe OSA.[3] Only 10% of patients with OHS do not have OSA but rather have non-obstructive sleep hypoventilation.[4–6] OHS is prevalent, and if untreated, can lead to significant adverse outcomes, increasing risk of hospitalisation and death,[7–12] likely because of respiratory and cardiovascular complications.[12–15] The prevalence of OHS is likely to increase globally with the increasing prevalence of severe obesity.[16–18]

Over the past decade, increasing attention has been paid to the evaluation and management of OHS; rising rates of global obesity along with greater awareness of the significant health and social costs of this disorder have been

Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; CO_2, carbon dioxide; CPAP, continuous positive airway pressure; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PAP, positive airway pressure; PaO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; NIV, noninvasive ventilation.

* Corresponding author.
E-mail address: fmasa@separ.es (J.F. Masa Jiménez).

https://doi.org/10.1016/j.pulmoe.2020.05.012

Table 1 Diagnostic criteria of OHS. The OHS diagnosis is clinical; the complementary findings could be present or not in all OHS patients, so are not necessary to establish the diagnosis of OHS.

Diagnostic criteria of OHS	
Clinical diagnostic	(A) BMI > 30 kg/m^2
	(B) $PaCO_2$ > 45 mmHg measured by arterial blood gasometry
	(C) Exclude other causes of hypoventilation
Complementary	(A) Serum bicarbonate level > 27 mEq/L
	(B) Hypoxaemia during wakefulness measured by pulse oximetry
Sleep study test	(A) Polysomnography or respiratory polygraphy to identify phenotype of OHS based on severity of OSA and the degree of hypoventilation during sleep with transcutaneous CO_2 or end tidal CO_2

BMI: body mass index; CO_2: carbon dioxide; OSA: obstructive sleep apnea; OHS: obesity hypoventilation syndrome; $PaCO_2$: partial pressure of carbon dioxide. Authors: Victor R. Ramírez Molina; Juan F. Masa Jiménez.

driving factors fuelling interest in how best to manage those with OHS.[19]

The evaluation, management and treatment of OHS must be multidisciplinary and as such should include expertise from chest physicians, sleep specialists, cardiologists, nutritionists and/or bariatricians; most treatment strategies focus on treating sleep-disordered breathing (SDB) with positive airway pressure (PAP) therapy during sleep, as opposed to aiming to reduce cardiovascular risk profile, also include lifestyle changes, weight loss, bariatric surgery and rehabilitation programmes.[20] See Fig. 1.

In this review we will explore treatment of OHS in the different modalities, with special attention on PAP treatment.

Weight loss and bariatric surgery

Despite appropriate adherence to PAP therapy, multiple studies have shown that cardio-metabolic risk factors of severe obesity are persistent,[3,21,22] with also occurs with cardiovascular morbidity and mortality, remaining high in patients with OHS.[23–25]

Weight loss continues to be the ideal treatment, as it has been proven to improve diurnal respiratory failure, pulmonary hypertension, sleep-disordered breathing as well as improvements in cardiovascular and metabolic outcomes.[4,26] It has been suggested that loss of 25–30% of actual body weight can lead to the resolution of the OHS.[20,26] However, it is difficult to achieve and maintain this degree of weight loss without bariatric surgery.[26] When compared to non-surgical methods of weight loss, bariatric surgery has proven to be much more effective for sustained weight loss in patients who suffer from severe obesity (BMI > 40 kg/m^2).

Bariatric interventions are effective in achieving significant, sustainable, weight loss that can improve cardiovascular and metabolic outcomes. The safety of bariatric procedures has improved over time; most recent clinical trials have reported improvements in metabolic and cardiovascular morbidities and reductions in all-cause and cardiovascular mortality in patients undergoing laparoscopic sleeve gastrectomy or gastric bypass surgery.[26] Laparoscopic sleeve gastrectomy, Roux-en-Y gastric bypass or biliopancreatic diversion with duodenal switch are more likely to lead to the magnitude of weight loss necessary to lead to the resolution of OHS than laparoscopic gastric banding.[26]

A systematic review and meta-analysis in 2014[27] examined effectiveness and risks of bariatric surgery; gastric bypass was shown to be the most effective method to date regarding weight loss but has proved to be associated with more complications as well. Data has shown adjustable gastric banding to have a lower mortality and complication rates, yet the reoperation rate presented by the patients was higher and weight loss was less substantial than gastric bypass; sleeve gastrectomy appeared to be more effective in weight loss than adjustable gastric banding and comparable to gastric bypass.

Another systematic review[20] examined whether a weight loss intervention should be performed in patients with OHS; the studies found that a comprehensive weight loss programme (including motivational counselling, dieting, and exercise) can reduce weight by 6–7%, but confers no clinically significant effects compared to standard care. Bariatric surgery, on the other hand, is associated with more robust weight loss (15–64.6% depending on the type of intervention), reduction of obstructive sleep apnea severity (18–44% reduction of the AHI (apnea–hypopnea index)), and improvement in gas exchange (17–20% reduction in $PaCO_2$), ultimately leading to the resolution of OHS. Moreover, daytime sleepiness and pulmonary artery pressure also improve with significant weight loss. Bariatric surgery is associated with adverse effects in roughly one-fifth of patients, but serious adverse effects are very rare. The level of certainty in the estimated effects has shown to be very low for most adverse outcomes.

The impact of bariatric surgery on improving OSA using the metric of AHI has presented a high rate in variations. In a meta-analysis of 12 studies, which included a total of 342 patients, Greenburg et al. showed a decrease in the AHI of 55 episodes/h to 16 episodes/h in patients with OSA and severe obesity; however, many of these patients remained with moderate or worse OSA (AHI > 15 episodes/h) and therefore continue to require treatment for OSA.[28] In patients with OHS, 14% continue to require positive airway pressure treatment after surgical weight loss.[29] Despite numerous claims in the lay press that bariatric surgery can cure OSA, several studies have shown that OSA may persist following weight loss. Recurrence or worsening of sleep apnea has been observed following an initial weight reduction even without a concomitant weight increase. The most important predictor of OSA severity following weight loss is the preoperative severity of disease, as measured by the AHI.[30,31]

There are limited long-term data on the efficacy of bariatric surgery in OHS[29] and it is not a safe option for

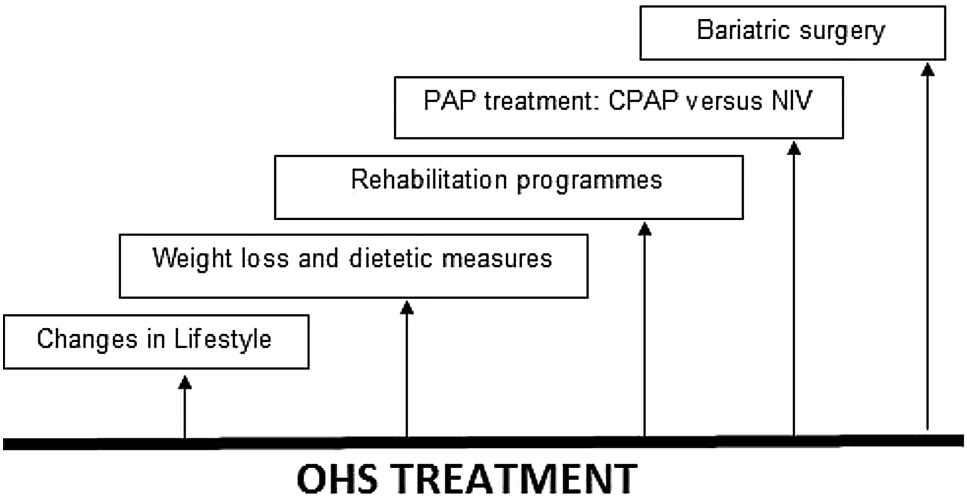


Figure 1 Treatment in OHS. OHS must be treated multidisciplinary, including lifestyle changes, dietetic measures and weight loss, rehabilitation programmes, PAP treatment (CPAP or NIV) and bariatric surgery (especially for younger patients). *Abbreviations*: CPAP: continuous positive airway pressure; NIV: noninvasive ventilation; PAP: positive airway pressure; OHS: obesity hypoventilation syndrome. Authors: Victor R. Ramírez Molina; Juan F. Masa Jiménez.

some patients with significantly increased perioperative risk.[32] The perioperative adverse events include venous thromboembolism, surgical reintervention, and prolonged hospital stay.[33,34]

Some degree of weight regain (>15% gain of initial weight loss postbariatric surgery) occurs in 25%–35% of patients 2–5 years after bariatric surgery[35–37]; the recurrence of OHS with this level of weight gain remains unclear.

The guideline panel of a systematic review in 2020 made a conditional (i.e. weak) recommendation suggesting a weight loss intervention for patients with OHS. This recommendation was based on very low-quality evidence. Although the weight loss target is based upon the observation that greater weight loss is associated with better outcomes, there is a need for better quality studies to ascertain the degree of weight loss necessary to achieve improvement in clinically relevant outcomes in patients with OHS.[20]

Rehabilitation programmes

The data regarding randomised clinical trials of weight loss targeted rehabilitation programmes for patients with OHS is very limited; pulmonary rehabilitation is an established form of treatment for patients with chronic pulmonary disease, thus similar programmes with particular emphasis on obesity can be expected to benefit patients with OHS. To further reduce the high cardiovascular and metabolic burden in OHS, there is a need for a multimodal a therapeutic approach combining home NIV/CPAP with lifestyle interventions and rehabilitation programmes.[38]

In a small pilot clinical trial,[39] 3 months of a multimodal hybrid inpatient-outpatient motivation, exercise and nutrition rehabilitation programme was added to home NIV therapy, compared to just NIV therapy, the addition of this comprehensive rehabilitation programme led to greater weight loss, exercise capacity and improved quality of life at 3 months while the participants were actively enrolled in the 3-month programme; However, these benefits were not sustained at 12 months.

Supplemental oxygen therapy

In approximately 20%–30% of patients with OHS, hypoxaemia during sleep persists despite adequate titration of NIV or CPAP.[40] High concentration of supplemental oxygen (i.e. 100% or 50% FiO_2) without positive pressure therapy can lead to increased hypoventilation and worsening of hypercapnia in patients with OHS[41,42]; however, the effect of lower concentrations of supplemental oxygen added to PAP therapy remains unclear. The effect of 2 months of supplemental oxygen therapy added to PAP therapy (CPAP or NIV) was examined in a post hoc analysis of 302 patients.[43] In the NIV group, supplemental oxygen was associated with a reduction in the systolic blood pressure. However, the reduction in body weight could have partially confounded this effect. Oxygen added to CPAP was associated with increased frequency of morning confusion. In the lifestyle modification group (i.e. no PAP therapy), supplemental oxygen therapy was associated with compensatory metabolic alkalosis and a decrease in the AHI. In aggregate, 2 months of oxygen therapy was associated with marginal changes that were insufficient to consider it either beneficial or harmful.[43] Long-term studies examining the role of oxygen therapy alone or added to PAP therapy are necessary.

In a double-blind, randomised, controlled, crossover trial, 24 outpatients newly diagnosed with OHS inhaled 100% oxygen or room air for 20 min on 2 separate days; the study showed that breathing 100% oxygen causes worsening hypercapnia in stable patients with OHS.[41] Later, in a double-blind randomised crossover study, OHS patients breathed oxygen concentrations (FiO_2 0.28 and 0.50), each for 20 min, separated by a 45 min washout period. The study investigated the effects of moderate concentrations of supplemental oxygen on PCO_2, pH, minute ventilation among people with stable untreated OHS, with comparison to healthy controls. The findings concluded that among people with mild, stable untreated OHS, breathing moderate concentrations of supplemental oxygen increased $PaCO_2$, sufficient to induce acidaemia during FiO_2 0.50.[42]

Positive airway pressure therapy

OHS is treated with positive airway pressure (PAP) therapy during sleep. The two most commonly used PAP modalities are continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV). Although CPAP can splint the upper airway open and effectively treat OSA, it does not increase ventilation as effectively as NIV does.[44]

The short-term benefits of CPAP include improvement in gas exchange and sleep-disordered breathing[45] with an observed response between 50% and 80% of cases although it may vary in the sleep apnea severity and the time of follow-up. This improvement is directly proportional to the hours of CPAP use, as each hour of use of PAP therapy decreased the $PaCO_2$ by 1.8 mmHg and the PaO_2 increased by 3 mmHg.[40]

PAP therapy improves gas exchange, respiratory sleep disorders and probably lung function and central respiratory impulse to carbon dioxide (CO_2). Night-time hypoventilation can be effectively improved, but not in all cases,[46–49] and daytime $PaCO_2$ reduced or restored to normal values.[48] The effectiveness of NIV has been assessed in several long-term, observational studies[1,7,23,44,50–55] and medium-term randomised trials.[3,21,56]

In patients with OHS and severe OSA, medium-term randomised controlled trials[7,38,50,57–59] and a long-term clinical trial[24,26,60] have shown CPAP and NIV to be equally effective in improving symptoms, quality of life and sleep, gas exchange during waking and sleep, as well as spirometric and polysomnographic parameters.

Mechanisms of improvement in hypercapnia with PAP use

The mechanisms by which diurnal hypercapnia improves with PAP are complex and not fully understood. PAP therapy can influence the following mechanisms: abnormal respiratory mechanics, central responses to hypercapnia and/or neurohormonal dysfunction (leptin resistance) and sleep-disordered breathing.[61] See Table 2.

NIV can reduce inspiratory muscular activity,[62] so that it can efficiently decrease the mechanical load favouring muscular rest and greater muscular efficacy during the day after nocturnal NIV treatment. Continuous positive airway pressure and NIV may decrease the mechanical load avoiding upper airway repetitive obstructions during sleep.

As for leptin resistance, the levels of serum leptin decrease to normal limits in patients with OSA treated with CPAP,[63,64] but it is assumed that apneas and hypopneas are the cause of the elevated leptin levels rather than being the result of them.[65,66] Leptinaemia also decreases with NIV treatment[67,68] as does daytime hypercapnia, and some studies have shown a correlation between leptinaemia and a reduction in the hypercapnic ventilatory response,[69] while another study[68] reported contradictory results, i.e., an increase of leptin with NIV. Therefore, the role of leptin in how NIV treatment achieves improvement, is still unclear.

Finally, in regards to sleep-disordered breathing, repetitive obstructive events produce increasing hypercapnia, not resolved with the hyperventilation that occurs at the end of obstructive events. Despite correction of these nocturnal obstructive events with CPAP, daytime $PaCO_2$ does not return to normal in all cases. Several studies have highlighted that the CPAP response may vary depending on the predominance of nocturnal obstructive events[10,44] and the time of follow-up because CPAP may have a delay in its efficacy related to NIV.[22] Non-invasive ventilation has shown to prevent obstructive events and reduce hypoventilation during sleep (including rapid eye movement [REM] sleep). Both NIV and CPAP should decrease nocturnal hypercapnia, leading to lower daytime serum bicarbonate and consequently less blunting of the central carbon dioxide response.[70]

Scientific research base

There are several randomised controlled studies that compare different treatments in OHS.[3,22,24,56,71] One of these studies compared the short-term efficacy of NIV and CPAP treatments in 36 patients with OHS selected in considering their favourable response to a night of CPAP treatment.[71] After 3 months, the improvements in daytime sleepiness and in clinical and gas exchange parameters were similar between CPAP and NIV groups.

In another trial including 38 patients with mild hypercapnia with NIV compared to a control group treated with conservative measures, the NIV group had a significant reduction in daytime $PaCO_2$, bicarbonate and an increase in pH. Therapy with NIV, as expected, was associated with a great improvement in all sleep variables analysed, sleep architecture, average oxygen saturation, oxygen saturation time less than 90%, apnea and hypopnea index, with a positive and significant correlation between average oxygen saturation during sleep and diurnal arterial blood gases. In contrast, no change was observed in any of the metabolic and inflammatory parameters studied, but the follow-up was only one month, so no other conclusions could be drawn.[21] In this study, the patients had a lower BMI and were less hypercapnic than the subjects included in other trials.[3,71]

The Pickwick project is the largest multicenter randomised controlled trial designed to assess medium-term (two months) effectiveness of NIV, CPAP, and lifestyle modification (control group) and long-term (3 years) effectiveness between NIV and CPAP in OHS[65,72]; there are two clinical trials in parallel depending on the existence or absence of severe OSA (AHI $\geq$ 30). The trial which includes severe OSA has three arms: NIV, CPAP and change in lifestyle for two months (first phase). After this period of time, the lifestyle change group was re-randomised to NIV or CPAP to continue at least 36 months (second phase). Patients with an AHI < 30 were randomised to NIV or change in lifestyle for at least 36 months (second phase), although an evaluation of results was performed at two months (first phase). The results of the first phase were entirely published.[3] The first publication included 221 patients with severe OSA randomised to NIV, CPAP and change in lifestyle; $PaCO_2$ who improved with each of the three treatments, but the improvement was greater with the use of NIV, with a significant difference in relation to the group of conservative measures. In the CPAP group, the reduction of $PaCO_2$ depended on compliance with the treatment. Thus, NIV and CPAP decreased blood bicarbonate levels but after adjusting baseline data only NIV achieved statistical significance compared to the control group. Sleep variables improved notably with the

Table 2 Potential mechanism of improvement with PAP therapy in OHS. PAP therapy can influence in the following mechanisms to improve daytime hypercapnia: mechanical load, leptine resistance and breathing sleep disorder; including reduce inspiratory muscular activity favouring muscular rest, decrease in central resistance leptine and decrease in nocturnal obstructive events and sleep hypercapnia.

Mechanism of diurnal hypercapnia	Influence and effect of PAP treatment
1. Abnormal respiratory mechanics	NIV can reduce inspiratory muscular activity. Decrease the mechanical load favouring muscular rest and greater muscular efficacy. NIV and CPAP may decrease the mechanical load avoiding upper airway repetitive obstructions during sleep.
1. Central responses to hypercapnia and/or neurohormonal dysfunction (leptin resistance)	NIV and CPAP decrease to normal limits the levels of serum leptin; reduction in the hypercapnic ventilatory response.
2. Sleep-disordered breathing	NIV and CPAP correct the obstructive events (apneas and hypopneas). NIV can prevent obstructive events and reduce hypoventilation during sleep (including REM sleep).

CPAP: continuous positive airway pressure; NIV: noninvasive ventilation; OHS: obesity hypoventilation syndrome; PAP: positive airway pressure; REM: rapid eye movement. Authors: Victor R. Ramírez Molina; Juan F. Masa Jiménez.

use of NIV and CPAP, both proving to be equally efficient and with little or no difference between the two; only the NIV group presented an increase in the FVC, FEV_1 values and the 6-minute walk test. In another publication of this Pickwick study, 86 patients were randomised and treated for two months with NIV or lifestyle modifications.[56] The NIV group significantly improved $PaCO_2$ and serum bicarbonate levels compared to the control group.

In another randomised controlled trial, NIV or CPAP was used for 3 months with 60 participants. The primary objective was to identify the frequency of treatment failure defined as, hospital admission, persistent ventilatory insufficiency or lack of adherence, while secondary objectives included life quality related to health and drowsiness. A total of 57 patients completed the follow-up without differences in treatment failure between the groups (NIV 14.8% versus CPAP 13.3%; $p = 0.87$). It is worth noting that adherence to treatment and $PaCO_2$ in wakefulness at three months were similar (NIV 5.3 h/night; CPAP 5.0 h/night; $p = 0.62$, and $PaCO_2$ in wakefulness at three months of 44, 2 and 45.9 mmHg, respectively; $p = 0.60$). The differences between the groups in the improvement of sleepiness and the life quality were not significant. Baseline severity of ventilatory failure (based on $PaCO_2$ levels) was the only significant predictor for such insufficiency after a three months periods of the study (OR, 2.3; $p = 0.03$).[22]

The multicentre, open-label, randomised controlled Pickwick trial published its long-term results on 97 OHS patients with severe OSA treated with NIV and 107 treated with CPAP.[24] The median follow-up was 5.44 years (interquartile range [IQR] 4.45–6.37) for all patients, 5.37 years (4.36–6.32) in the CPAP group, and 5.55 years (4.53–6.50) in the NIV group. The hospitalisation days per patient-year were 1.63 (standard deviation [SD] 3.74) in the CPAP group and 1.44 (3.07) in the NIV group (adjusted rate ratio 0.78, 95% CI 0.34–1.77; $p = 0.561$). Changes in other hospital resource utilisation, blood pressure, arterial blood gases, spirometry, quality of life, clinical symptoms and supplemental oxygen therapy remained similar between PAP modalities. Both NIV and CPAP also similarly improved the pulmonary artery pressure and diastolic left ventricular dysfunction.[72] Given that CPAP has lower complexity and cost, CPAP might be the preferred first-line PAP treatment modality.[24]

Cost-effectiveness of PAP therapy modalities

CPAP is simpler to implement and is less costly than NIV.[24] To investigate which of the two treatments is more cost-effective, the only study reported is from Masa and cols, whom carried out a post hoc, within-trial, cost-effectiveness analysis using the large multicentre, open-labelled, randomised controlled study (Pickwick study)[3,24,43,56,65,73,74]; the aim was to determine the comparative cost-effectiveness relationship between NIV and CPAP based on 3 years of follow-up, using hospitalisation days as the primary outcome measure in a cost-effectiveness analysis, or considering the hospitalisation days in monetary terms where the value of a hospitalisation day is approximately its cost, in a cost–benefit analysis.

In total, 363 patients were selected, 215 were randomised and 202 were available for the analysis. The median (IQR) follow-up was 3.01 (2.91–3.14) years for NIV group and 3.00 (2.92–3.17) years for CPAP. The mean (SD) Bayesian estimated hospital days was 2.13 (0.73) for CPAP and 1.89 (0.78) for NIV. The mean (SD) Bayesian estimated cost per patient/year in the NIV arm, excluding hospitalisation costs, was €2075.98 (91.6), which was higher than the cost in the CPAP arm of €1219.06 (52.3); mean difference €857.6 (105.5). CPAP was more cost-effective than NIV (99.5% probability) because longer hospital stay in the CPAP arm was compensated for by its lower costs. Similar findings were observed in the high and low adherence subgroups; Thus, the conclusion of this study is that CPAP is more cost-effective than NIV; therefore, CPAP should be the preferred treatment for patients with OHS with severe OSA.[75]

Initial PAP treatment suggestion

CPAP should be the initial treatment modality in patients with OHS if severe OSA is present, due to its relative simplicity, low cost and efficacy.[4,46,75] In patients with OHS without severe OSA, NIV is the preferred PAP modality, because in these patients without a significant number of obstructive

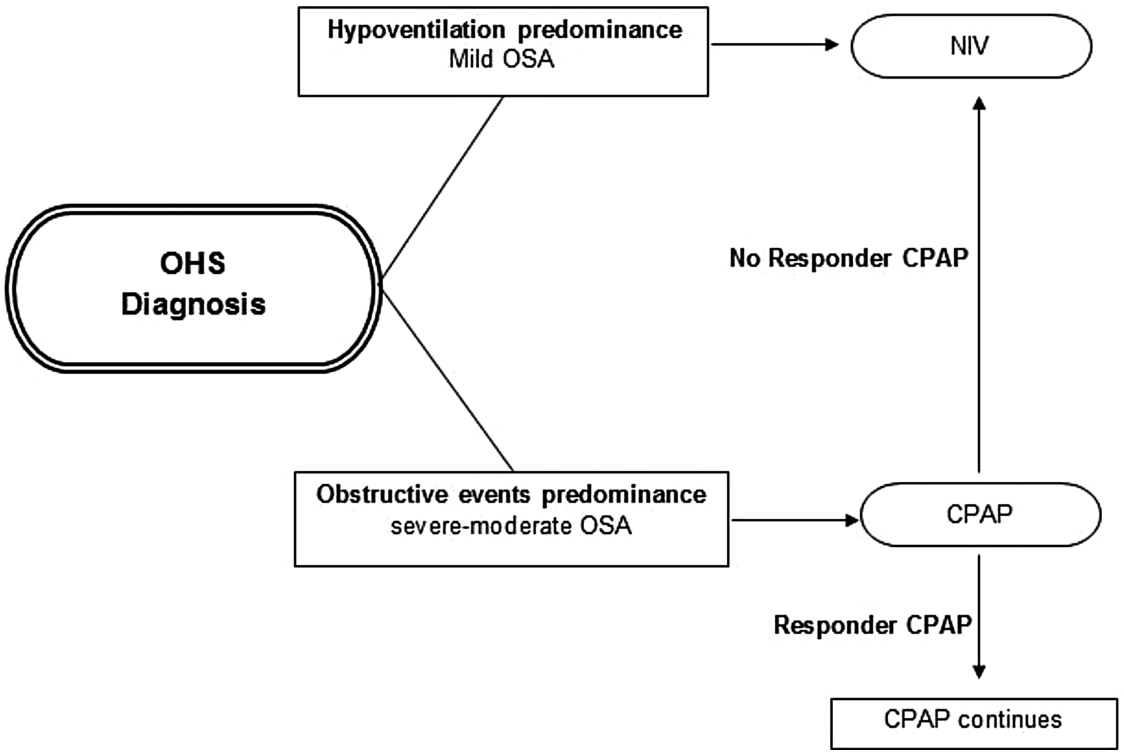


Figure 2 Initial PAP treatment election in OHS. CPAP should be the initial modality treatment if the main cause of diurnal hypoventilation is the predominance of obstructive events (severe–moderate OSA) and if in subsequent evaluations at 1–3 months the patient responds with adequate oxygenation (PaO_2) and ventilation ($PaCO_2$) the CPAP should be continued; if the patient does not responds or if the OHS patient has hypoventilation predominance (mild OSA), NIV should be the initial modality treatment preferred. *Abbreviations*: CPAP: continuous positive airway pressure; NIV: noninvasive ventilation; OHS: obesity hypoventilation syndrome; OSA: obstructive sleep apnea; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; PAP: positive airway pressure. Authors: Victor R. Ramírez Molina; Juan F. Masa Jiménez.

apneas and hypopneas, their nocturnal hypoventilation may depend on other mechanisms (e.g. obesity). See Fig. 2. However, a case by case evaluation is necessary to determine the initial treatment.[26]

In acute hypercapnic respiratory failure or hospitalised patients, NIV should be the first option, due to its potentially greater efficacy against hypoventilation and the underlying severity of respiratory failure.[61]

Conclusions

Obesity is a worldwide, increasingly ubiquitous health issue that has triggered the wide spread of several related medical conditions; OHS is one of the respiratory sleep disorders that has the greatest impact on increasing cardiovascular risk. Therefore, OHS must be recognised promptly, and optimally treated; a multidisciplinary approach is likely to be more effective for improving long-term outcomes, including loss weight, rehabilitation programmes and PAP therapy; CPAP should be the initial treatment when indicated.

Authors' contributions

All authors equally contributed to this paper with conception and design of the study, literature review, critical revision, editing and final approval of the final version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

None declared.

References

1. Borel JC, Burel B, Tamisier R, Dias-Domingos S, Baguet JP, Levy P, et al. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. PLoS One. 2013;8:e52006.
2. Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest. 2001;120:369–76.
3. Masa JF, Corral J, Alonso ML, Ordax E, Troncoso MF, Gonzalez M, et al. Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick study. Am J Respir Crit Care Med. 2015;192:86–95.
4. Olson AL, Zwillich C. The obesity hypoventilation syndrome. Am J Med. 2005;118:948–56.
5. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007;11:117–24.

6. Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med. 2011;183:292–8.
7. Priou P, Hamel J-F, Person C, Meslier N, Racineux JL, Urban T, et al. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest. 2010;138:84–90.
8. Berg G, Delaive K, Manfreda J, Walld R, Kryger MH. The use of health-care resources in obesity hypoventilation syndrome. Chest. 2001;120:377–83.
9. Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. Thorax. 2011;66:560–6.
10. Pérez de Llano LA, Golpe R, Ortiz Piquer M, Veres A, Vázquez M, Caballero O, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity hypoventilation syndrome. Chest. 2005;128:587–94.
11. Ojeda Castillejo E, de Lucas Ramos P, López Martin S, Resano Barrios P, Rodríguez Rodríguez P, Morán Caicedo L. Noninvasive mechanical ventilation in patients with obesity hypoventilation syndrome: long-term outcome and prognostic factors. Arch Bronconeumol. 2015.
12. Nowbar S, Burkart KM, Gonzales R, Fedorowicsz A, Gonzansky WS, Gaudio JC, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004;116:1–7.
13. Zwillich CW, Sutton FD, Pierson DJ, Greagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. Am J Med. 1975;59:343–8.
14. MacGregor M, Block AJ, Ball WC. Topics in clinical medicine: serious complications and sudden death in the Pickwickian syndrome. Hopkins Med J. 1970;126:279–95.
15. Miller A, Granada M. In-hospital mortality in the Pickwickian syndrome. Am J Med. 1974;56:144–50.
16. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. JAMA. 2018;19:1723–5.
17. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA. 2016;315:2284–91.
18. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–8.
19. Piper A, Pepin JL, Hart N. Positive airway pressure in obesity hypoventilation syndrome: is it worth it? Thorax. 2020, http://dx.doi.org/10.1136/thoraxjnl-2019-214403, pii: thoraxjnl-2019-214403.
20. Kakazu MT, Soghier I, Afshar M, Brozek JL, Wilson KC, Masa JF, et al. Weight loss interventions as treatment of obesity hypoventilation syndrome. A systematic review. Ann Am Thorac Soc. 2020;17:492–502, http://dx.doi.org/10.1513/AnnalsATS.201907-554OC.
21. Borel JC, Tamisier R, Gonzalez-Bermejo J, Baguet JP, Monneret D, Arnol N, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. Chest. 2012;141:692–702.
22. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72:437–44.
23. Castro-Añón O, Pérez de Llano LA, De la Fuente Sánchez S, Golpe R, Méndez Marote L, Castro-Castro J, et al. Obesity-hypoventilation syndrome: increased risk of death over sleep apnea syndrome. PLoS One. 2015;10:e0117808.
24. Masa JF, Mokhlesi B, Benítez I, Gomez de Terreros FJ, Sánchez-Quiroga MA, Romero a, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. Lancet. 2019;27:1721–32.
25. Bouloukaki I, Mermigkis C, Michelakis S, Moniaki V, Mauroudi E, Tzanakis N, et al. The association between adherence to positive airway pressure therapy and long-term outcomes in patients with obesity hypoventilation syndrome: a prospective observational study. J Clin Sleep Med. 2018;14:1539–50.
26. Mokhlesi B, Masa JF, Brozek JL, Gurubhagavatula I, Murphy PB, Piper AJ, et al. Evaluation and management of obesity hypoventilation syndrome. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200:e6–24.
27. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surg. 2014;149:275–87.
28. Greenburg D, Lettieri C, Eliasson A. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. Am J Med. 2009;122:535–42.
29. Martí-Valeri C, Sabaté A, Masdevall C, Dalmau A. Improvement of associated respiratory problems in morbidly obese patients after open roux-en-y gastric bypass. Obes Surg. 2007;17:1102–10.
30. Pillarm G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight reduction increases 75 years after weight reduction surgery. Chest. 1994;106:1702–4.
31. Lettieri CJ, Eliasson AH, Greenburg DL. Persistence of obstructive sleep apnea after surgical weight loss. J Clin Sleep Med. 2008;4:333–8.
32. Sugerman HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. Am J Clin Nutr. 1992;55:597S–601S.
33. Fernández AJ, Demaria EJ, Tichansky DS, Kellum JM, Wolfe LG, Meador J, et al. Multivariate analysis of risk factors for death following gastric bypass for treatment of morbid obesity. Ann Surg. 2004;239:698–702.
34. Flum D, Belle SH, King WC, Wahed AS, Berk P, Chapman W, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med. 2009;361:445–54.
35. Bastos EC, Barbosa EM, Soriano GM, dos Santos EA, Lima SM. Determinants of weight regain after bariatric surgery. Arq Bras Cir Dig. 2013;26 Suppl.:26–32.
36. Marchesini SD, Bareta GA, Cambi MP, Marchesini JB. Endoscopic plasma argon coagulation in treatment of weight regain after bariatric surgery: what does the patient think about this? Arq Bras Cir Dig. 2015;27 Suppl.:47–50.
37. Cooper TC, Simmons EB, Webb K, Burns JL, Kushner RF. Trends in weight regain following Roux-en-Y gastric bypass (RYGB) bariatric surgery. Obes Surg. 2015;25:1474–81.
38. Masa F, Pépin J, Borel J, Mokhlesi B, Murphy PB, Sánchez-Quiroga MA. Obesity hypoventilation syndrome. Eur Repir Rev. 2019;28:180097.
39. Mandal S, Suh ES, Harding R, Vaughan-France A, Ramsay M, Connolly B, et al. Nutrition and exercise rehabilitation in obesity hypoventilation syndrome (NERO): a pilot randomised controlled trial. Thorax. 2018;73:62–9, http://dx.doi.org/10.1136/thoraxjnl-2016-209826.
40. Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani AA, Hassaballa HA, et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med. 2006;2:57–62.
41. Wijesinghe M, Williams M, Perrin K, Weatherall M, Beasley R. The effect of supplemental oxygen on hypercapnia in subjects

with obesity-associated hypoventilation: a randomized crossover clinical study. Chest. 2011;139:1018–24.
42. Hollier CA, Harmer AR, Maxwell LJ, Menadue C, Willson GN, Unger G, et al. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study. Thorax. 2014;69:346–53, http://dx.doi.org/10.1136/thoraxjnl-2013-204389.
43. Masa JF, Corral J, Romero A, Caballero C, Terán-Santos J, Alonso-Álvarez ML, et al. The effect of supplemental oxygen in obesity hypoventilation syndrome. J Clin Sleep Med. 2016;12:1379–88.
44. Berger KI, Ayappa I, Chatr-Amontri B, Marfatia A, Sorkin IB, Rapoport DM, et al. Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. Chest. 2001;120:1231–8.
45. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55:1347–62.
46. Chau EH, Mokhlesi B, Chung F. Obesity hypoventilation syndrome and anesthesia. Sleep Med Clin. 2013;8:135–47.
47. Lee WY, Mokhlesi B. Diagnosis and management of obesity hypoventilation syndrome in the ICU. Crit Care Clin. 2008;24:533–49.
48. Masa JF, Celli BR, Riesco JA, Sánchez de Cos J, Disdier C, Sojo A. Noninvasive positive pressure ventilation and not oxygen may prevent overt ventilatory failure in patients with chest wall diseases. Chest. 1997;112:207–13.
49. Hida W, Okabe S, Tatsumi K, Kimura H, Akasiba T, Chin K, et al. Nasal continuous positive airway pressure improves quality of life in obesity hypoventilation syndrome. Sleep Breath. 2003;7:3–12.
50. Basoglu OK, Tasbakan MS. Comparison of clinical characteristics in patients with obesity hypoventilation syndrome and obese obstructive sleep apnea syndrome: a case–control study. Clin Respir J. 2014;8:167–74.
51. Budweiser S, Riedl SG, Jörres RA, Heinemann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. J Intern Med. 2007;261:375–83.
52. de Lucas-Ramos P, de Miguel-Díez J, Santacruz-Siminiani A, González-Moro JMR, Buendía-García MJ, Izquierdo-Alonso JL. Benefits at 1 year of nocturnal intermittent positive pressure ventilation in patients with obesity hypoventilation syndrome. Respir Med. 2004;98:961–7.
53. Janssens JP, Derivaz S, Breitenstein E, De Mural B, Fitting JW, Chevrolet JC, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest. 2003;123:67–79.
54. Heinemann F, Budweiser S, Dobroschke J, Pfeifer M. Noninvasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. Respir Med. 2007;101:1229–35.
55. Windisch W, Quality of Life in Home Mechanical Ventilation Study Group. Impact of home mechanical ventilation on health-related quality of life. Eur Respir J. 2008;32:1328–36.
56. Masa JF, Corral J, Caballero C, Barrot E, Terán-Santos J, Alonso-Álvarez ML, et al. Noninvasive ventilation in obesity hypoventilation syndrome without severe sleep apnea. Thorax. 2016;71:899–906.
57. Castro-Añón O, Golpe R, Pérez-de-Llano LA, López MJ, Escalona EJ, Pérez R, et al. Haemodynamic effects of non-invasive ventilation in patients with obesity-hypoventilation syndrome. Respirology. 2012;17:1269–74.
58. Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. Ann Surg. 1988;207:604–13.
59. Kauppert CA, Dvorak I, Kollert F, Heinemann F, Jörres RA, Pfeifer M, et al. Pulmonary hypertension in obesity-hypoventilation syndrome. Respir Med. 2013;107:2061–70.
60. Soghier I, Brożek JL, Afshar M, Tamae M, Wilson KC, Masa JF, et al. Noninvasive ventilation versus CPAP as initial treatment of obesity hypoventilation syndrome: a systematic review. Ann Am Thorac Soc. 2019, http://dx.doi.org/10.1513/AnnalsATS.201905-380OC [Epub ahead of print].
61. Ramírez-Molina VR, Gómez-de-Terreros FJ, Barca-Durán J, Masa JF. Non-invasive positive airway pressure in obesity hypoventilation syndrome and chronic obstructive pulmonary disease: present and future perspectives. COPD. 2017;14:418–28.
62. Pankow W, Hijjeh N, Schüttler F, Penzel T, Becker HF, Peter JH. Influence of noninvasive positive pressure ventilation on inspiratory muscle activity in obese subjects. Eur Respir J. 1997;10:2847–52.
63. Ip MS, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. Chest. 2000;118:580–6.
64. Phipps PR, Starrit E, Caterson I, Grunstein RR. Association of serum leptin with hypoventilation in human obesity. Thorax. 2002;57:75–6.
65. López-Jiménez MJ, Masa JF, Corral J, Terán J, Ordaz E, Troncoso MF, et al. Mid- and long-term efficacy of non-invasive ventilation in obesity hypoventilation syndrome: the Pickwick's Study. Arch Bronconeumol. 2016;52:158–65.
66. Fitzpatrick M. Leptin and the obesity hypoventilation syndrome: a leap of faith? Thorax. 2002;57:1–2.
67. Yee BJ, Cheung J, Phipps P, Banerjee D, Piper AJ, Grunstein RR. Treatment of obesity hypoventilation syndrome and serum leptin. Respiration. 2006;73:209–12.
68. Redolfi S, Corda L, La Piana G, Spandrio S, Prometti P, Tantucci C. Long-term noninvasive ventilation increases chemosensitivity and leptin in obesity-hypoventilation syndrome. Respir Med. 2007;101:1191–5.
69. Campo A, Freihbeck G, Zulueta JJ, Iriarte J, Seijo LM, Alcaide AB, et al. Hypercapnic response in obese patients. Eur Respir J. 2007;30:223–31.
70. Mokhlesi B, Tulaimat A, Faibursowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007;11:117–24.
71. Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax. 2008;63:395–401.
72. Masa JF, Mokhlesi B, Benitez I, Mogollon MV, Gomez de Terreros FJ, Sánchez-Quiroga MA, et al. Ecocardiographic changes with positive airway pressure therapy in obesity hypoventilation syndrome: long-term Pickwick randomized controlled trial. AM J Respir Crit Care Med. 2019, http://dx.doi.org/10.1164/rccm.20199061122OC.
73. Masa JF, Corral J, Romero A, Caballero C, Terán-Santos J, Alonso-Álvarez ML, et al. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. Chest. 2016;150:68–79.
74. Corral J, Mogollon MV, Sánchez-Quiroga M-Á, Gómez de Terreros J, Romero A, Caballero C, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018;73:361–8.
75. Masa JF, Mokhlesi B, Benítez I, Gómez de Terreros FJ, Sánchez-Quiroga M-Ángeles, Romero A, et al. Cost-effectiveness of positive airway pressure modalities in obesity hypoventilation syndrome with severe obstructive sleep apnoea. Thorax. 2020:1–9, http://dx.doi.org/10.1136/thoraxjnl-2019-213622.

Pulmonol. 2020;**26(6)**:378–385

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

The validity of surface EMG of extra-diaphragmatic muscles in assessing respiratory responses during mechanical ventilation: A systematic review

H.Y. AbuNurah[a,*], D.W. Russell[b], J.D. Lowman[c]

[a] *Department of Respiratory Therapy, King Saud bin Abdulaziz University for Health Sciences, KSA & the PhD in Rehabilitation Science Program, University of Alabama at Birmingham, Birmingham, AL, USA*
[b] *Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham, USA*
[c] *Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL, USA*

Received 1 August 2019; accepted 11 February 2020
Available online 2 April 2020

KEYWORDS
surface electromyography;
mechanical ventilation;
diaphragm;
respiratory muscles;
extra-diaphragmatic muscles;
respiratory mechanics

Abstract
Purpose: Evidence supporting the utilization of surface EMG (sEMG) of extra-diaphragmatic muscles for monitoring of mechanical ventilation (MV) assistance is unclear. The purpose of this review was to assess the quality of literature available on using extra-diaphragmatic sEMG as an assessment technique of respiratory responses during MV.
Methods: Studies using sEMG of extra-diaphragmatic respiratory muscles during MV were selected by two independent researchers after performing a database search of PubMed, CINAHL, GOOGLE SCHOLAR. Exclusion criteria were studies of patients with neuromuscular disorders, receiving neuromuscular blocking agents, receiving non-invasive MV, using needle EMG, and studies written in languages other than English. Quality of identified studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). This study is registered with PROSPERO, number (CRD42018081341).

Abbreviations: ASV, Adaptive Support Ventilation; Edi, Electrical activity of the diaphragm; EMG, Electromyography; EMG_{MAX}, Maximum electrical activity; EMG_{MEAN}, Mean electrical activity; EMG_{MIN}, EMG activity in one minute; EMG_{Ti}, Duration of electrical activity; sEMG, Surface electromyography; ICU, Intensive Care Unit; MV, Mechanical ventilation; NAVA, Neural Assisted Ventilation; NRD, Neuro-respiratory drive; $P_{0.1}$, Occlusion pressure at 1 milliseconds; P_{di}, Trans-diaphragmatic pressure; P_{es}, Esophageal pressure; $\mathbf{P_{ETCO_2}}$, End tidal CO_2; PRISMA-DTA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy; PSV, Pressure Support Ventilation; PTP, Pressure-time product; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies; SCM, Sternocleidomastoid; SIMV, Synchronized Intermittent Mandatory Ventilation; TI_e, Mechanical duration of inspiratory effort; VAS, Visual Analog Scale; $\dot{V}_E$, Minute ventilation; WOB, Work of Breathing.

* Corresponding author at: Department of Physical Therapy, School of Health Professions, University of Alabama at Birmingham, SHPB 344, 1720 2ND AVE S, Birmingham, AL, USA.
E-mail address: hassan01@uab.edu (H.Y. AbuNurah).

https://doi.org/10.1016/j.pulmoe.2020.02.008

Results: 596 references were identified. Of the identified studies, 7 studies were included in the review. Findings demonstrate that sEMG of extra-diaphragmatic muscle activity is a valid and applicable tool to evaluate mechanical loading/unloading of respiratory muscles and respiratory drive or sensation. However, the quality of literature supporting sEMG as monitoring tool of respiratory responses were characterized by a high and unclear risk of bias.
Conclusions: Although it appears to be a valid and applicable tool, there is a scarcity of literature that directly demonstrates the diagnostic accuracy of sEMG of extra-diaphragmatic muscles in monitoring respiratory mechanics and respiratory drive or sensation during MV assistance across wide populations and conditions.

Introduction

Although mechanical ventilation (MV) is an essential life-saving therapy, it may result in a rapid diaphragmatic weakness due to its reduced activity.[1] Diaphragmatic disuse atrophy and protein proteolysis can occur rapidly during MV, resulting in a progressive diaphragmatic dysfunction.[1,2] Hence, tailoring MV assistance to the patients' needs is an important objective to maintain adequate diaphragmatic function and, thus, accelerating the MV liberation process.[3,4] This objective increases the need for rigorous assessment of patient-ventilator interaction.[5]

Increased work of breathing (WOB) is manifested by the use of respiratory extra-diaphragmatic muscles (e.g., external intercostal, parasternal intercostal, sternocleidomastoid, scalene) to compensate for the overload imposed on diaphragmatic capacity.[6–10] This sign becomes prominent as neuro-respiratory drive (NRD) increases in patients during MV liberation failure.[10–12] In other words, the increased activation of respiratory extra-diaphragmatic muscles is an attempt to achieve balance between mechanical load (demand) and respiratory muscle capacity (supply).[13]

NRD can be evaluated invasively via an esophageal EMG catheter placed at the level of the diaphragm[14]; this technique is associated with technical complexity and potential risks.[15,16] In contrast, the use of surface EMG (sEMG) of extra-diaphragmatic muscles is another method for assessing NRD which has been introduced as a promising assessment tool to evaluate respiratory loading/unloading and respiratory sensation during MV.[17–19]

The rationale behind using sEMG stems from its non-invasiveness and easy practical use.[20,21] These advantages are highlighted, as patients in the intensive care unit (ICU) are vulnerable to infections and at an increased risk of complications.[16,22] In addition, the activation of extra-diaphragmatic muscles when ventilatory demand outweighs ventilatory capacity makes these muscles a practical choice for the detection of increased loading and neural drive.[17] Also, the diaphragm moves significantly during inspiration, making it difficult to obtain accurate EMG signal from surface electrodes, whereas this is not an issue for extra-diaphragmatic muscles.[23]

Although sEMG has been used to detect clinical deterioration, inspiratory muscle fatigue, and respiratory muscle endurance,[24,25] the quality of evidence supporting its utilization with extra-diaphragmatic muscles during MV assistance is unclear. Therefore, the aim of this non-comparative systematic review is to assess the evidence supporting the use of extra-diaphragmatic sEMG to evaluate respiratory responses during MV assistance.

Methods

Given the novelty of using sEMG to assess respiratory mechanics with patients receiving MV, the database search was performed with no date restrictions (last search was completed October 2019). This review was prospectively registered with PROSPERO (CRD42018081341). A medical librarian was consulted and helped select appropriate databases and search terms. A comprehensive search was performed using the following databases: PubMed, CINAHL, and GOOGLE SCHOLAR. For example, in PubMed, the search strategy resulted in the following string: ''(respiratory muscles OR inspiratory muscles OR accessory muscles OR scalene OR sternocleidomastoid OR parasternal OR intercostal) AND (electromyography OR EMG) AND (mechanical ventilation OR artificial respiration) AND (muscle activity OR respiratory mechanics OR evaluation OR assessment).'' Medical Subject Headings (MeSH) were used to facilitate records identification. The same search terms were used in all databases, respecting the differences in search strategy for each one.

The inclusion criteria were (1) studies using sEMG (2) of extra-diaphragmatic muscles (3) during invasive MV, (4) in adolescent and adult patients ($\geq$13 years old). Studies were excluded based on the following exclusion criteria: (1) patients with neuromuscular disorders, (2) patients receiving neuromuscular blocking agents, (3) use of needle EMG, and (4) studies written in languages other than English.

Following the comprehensive search of databases, two independent reviewers screened titles and abstracts according to the inclusion criteria. Then, the selected studies went through full text screening to determine their eligibility for the review and therefore, data extraction. The studies were selected based on the consensus of the two reviewers (HYA and JDL); there were no disagreements necessitating a third reviewer. The main results of each of the selected articles were summarized and tabulated. Methodological quality of selected studies was assessed with the Quality Assessment

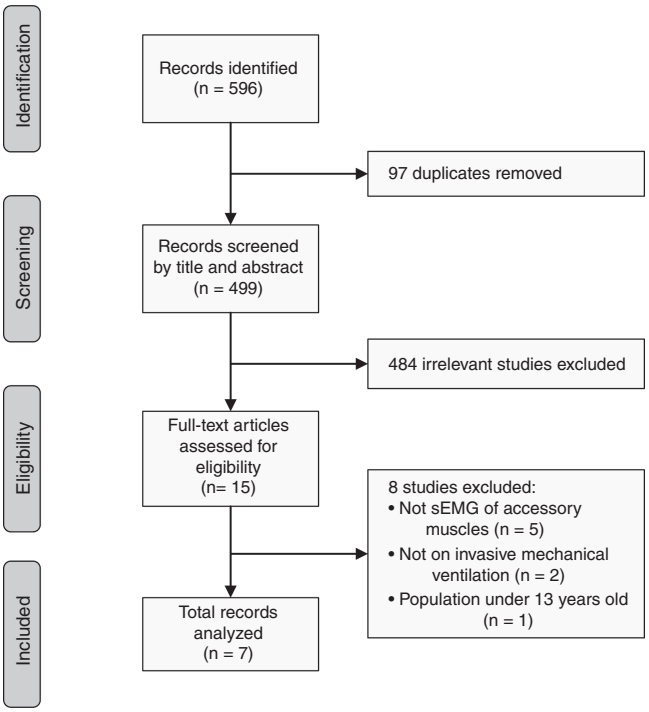


Figure 1 PRISMA Flow Diagram of the Selection Process and The Study Search Results.

of Diagnostic Accuracy Studies (QUADAS-2) tool, which is recommended for use in systematic reviews by Cochrane Collaboration.[22]

Results

The literature search yielded a total of 596 studies which were identified based on their titles and abstracts. The final included studies were defined by consensus of the two reviewers, and 7 studies were included in the present review (Fig. 1). The 7 studies were written by 6 different author groups. A single group of 3 researchers collaborated on 2 different studies that met the inclusion criteria of this review.[17,26] Three of the studies were conducted in France, 2 studies in Switzerland, 1 study in Germany, and 1 in Italy.

Heterogeneity of the methods used in the included studies and results presented precluded our planned meta-analysis. Hence, we described the studies qualitatively according to the first author and publication year, sample size, study design and population, type of intervention or MV settings, index tests, reference tests, and target conditions or responses. A summary of the results is described in the Table 1 provided following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA).[27]

Maximum EMG activity (EMG_{MAX} or $EMG_{MAX\%}$) was a commonly used parameter to assess muscle activity (n = 5); this value represents EMG activity relative to the peak EMG signal obtained during any inspiratory effort.[17,28–31] EMG area under the curve (EMG_{AUC}) was used in 3 studies[17,26,32]; this is the mathematical integral of the absolute value of raw EMG signals, expressed as a proportion of the maximum value. Duration of EMG activation (EMG_{Ti}) was reported in 1 study for SCM.[30] EMG activity per minute (EMG/min), was calculated as EMG_{AUC} x (total respiratory rate).[17] Mean EMG activity (EMG_{MEAN}; average EMG activity during 40 respiratory cycles), and EMG_{MAX}-EMG_{MIN} ($EMG_{MAX-MIN;}$ during 40 respiratory cycles) were reported in 1 study.[28]

Extra-diaphragmatic muscles tested were: sternocleidomastoid (SCM) (n = 4 studies),[28,30–32] parasternal (n = 3),[17,28,29] scalene (n = 2),[17,26] and ala-nasi (n = 2).[17,26] Of the included studies, diaphragmatic activity was assessed via invsavie espohageal catheter (Edi) in 4 studies[26,28,30,31] and via sEMG in 2 studies.[28,29]

All of the included studies were prospective and used pressure support ventilation (PSV) as a spontaneous mode of MV for weaning, or incorporated PSV with the use of synchronized intermittent mandatory ventilation (SIMV; n = 2),[30,32] adaptive support ventilation (ASV; n = 1),[32] neurally adjusted ventilatory assist (NAVA; n = 1).[26] Study populations mainly included subjects with respiratory failure due to various cardiopulmonary conditions and/or prolonged MV.

sEMG of extra-diaphragmatic muscles and respiratory conditions

All studies used sEMG to detect respiratory muscle responsiveness to varying levels of MV support, modes, or body positions. We found that sEMG of extra-diaphragmatic muscles was used as a surrogate tool to monitor two main respiratory responses or target conditions: mechani-

Table 1 Overview of sEMG Index Tests and Its Assessment Ability of Respiratory Mechanics and Respiratory Sensation.

Study	(Sample Size) & Population	Intervention & Design	Muscle: EMG Index Test	Reference Standard	Target Response	
					Respiratory Mechanics (Loading/Unloading)	Respiratory Sensation (Dyspnea)
Brochard et al. (1989)	(N = 8) subjects with RF & PMV	4 levels of MV support (PSV 0 - 15 cmH_2O), prospective cohort	SCM: EMGMAX	RR, V_T, V_E, Pdi, Edi, $\triangle$Pes - $\triangle$V, $\dot{V}_{O_2}$, & diaphragm H/L frequency ratio	+	N/A
Imsand et al. (1994)	(N = 5) subjects with RF	3 levels of MV support (During SIMV-PSV mode: Low, medium & high), prospective cohort	SCM: EMGMAX & $EMGT_i$	RR, V_T, V_E, PTP, Edi, $\triangle$Pes - $\triangle$V, diaphragmatic EMG_{Ti} and TI_e, & $P_{0.1}$	+	N/A
Tassaux et al. (2002)	(N = 10) subjects with RF	Equal levels of MV support (during SIMV-PS & ASV modes), prospective cohort	SCM: EMGAUC	RR, V_T, V_E, & $P_{0.1}$	+	N/A
Schmidt et al. (2013)	(N = 12) subjects with RF	2 low & 2 high levels 0f MV support (PSV 6-12 ml/kg), prospective cohort	Para, scalene & ala-nasi: EMGMAX , EMG/min & EMGAUC	RR, Vt, PVA & VAS-dyspnea	+	+
Cecchini et al. (2014)	(N = 12) subjects with RF & PMV	7 levels of MV support (during PSV & NAVA 7-20 cmH_2O), prospective cohort	Scalene & ala-nasi: EMGAUC	RR, V_T, Edi & P_{ETCO_2}	+	N/A
Walterspacher et al. (2016)	(N = 9) subjects with RF & PMV	PCV & PSV at different body position, prospective cohort	Para: EMGMAX	RR, Borg scale & diaphragmatic sEMG	N/A	+
Bellani et al. (2018)	(N = 14) subjects with RF	3 levels MV support (during PSV changing by 4 cmH_2O), prospective cohort	Para & SCM: EMGMAX, EMG/min & EMGMEAN	Pmus, Edi & diaphragmatic sEMG	N/A	N/A

N/A, data not available, + responsive; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory ventilation; ASV, adaptive synchronized ventilation; NAVA, neurally adjusted ventilatory assist; PCV, pressure control ventilation; COPD, chronic obstructive pulmonary disease; RF, respiratory failure; PMV, prolonged mechanical ventilation; SCM, sternocleidomastoid; para, parasternal; EMG_{MAX}, maximum EMG activity; EMG_{AUC}, EMG area under the curve; EMG/min, EMG activity per minute; EMG_{MIN}, minimum EMG activity; EMG_{MEAN}, mean EMG activity; $EMG_{MAX-MIN}$, maximum-minimum EMG activity; Pdi, trans-diaphragmatic pressure; Edi, electrical activity of the diaphragm; RR, respiratory rate; V_T, tidal volume; $\dot{V}_E$,minute ventilation; $\dot{V}_{O_2}$, oxygen uptake; $P_{0.1}$, occlusion pressure at 1 milliseconds; PTP, pressure time product; $\triangle$Pes –$\triangle$V, esophageal pressure – volume curve; EMG_{Ti}, duration of electrical activity; TI_e mechanical duration of inspiratory effort; H/L, high/low; VAS, visual analogue scale; PVA, patient-ventilator asynchrony; Pmus, inspiratory muscle pressure; P_{ETCO_2}, end tidal carbon dioxide.

cal loading/unloading of respiratory muscles and respiratory sensation or dyspnea.

Data showed that extra-diaphragmatic muscle activity was responsive to mechanical loading/unloading and/or respiratory sensation during MV assistance (Table 1). Physiological measurements referenced to the response of sEMG activity that may reflect mechanical loading/unloading of respiratory muscles include: respiratory rate (RR), tidal volume (V_T), minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), WOB (quantified by esophageal pressure (P_{es}) plotted against volume (V) during active and passive breathing), end-tidal CO_2 (P_{ETCO_2}), diaphragmatic activity measured via Edi, diaphragmatic activity measured with sEMG, high/low diaphragmatic EMG frequency ratio (to detect diaphragmatic fatigue), pressure-time product (PTP) (calculated by (P_{es}) plotted against Time (T)), and trans-diaphragmatic pressure (P_{di}) (calculated by gastric pressure – Pes), mechanical duration of inspiratory effort (TI_e) and EMG duration (EMG_{Ti}) of the diaphragm. Physiological measurements referenced to sEMG in monitoring respiratory sensation include: visual analog scale (VAS) and Borg scale.

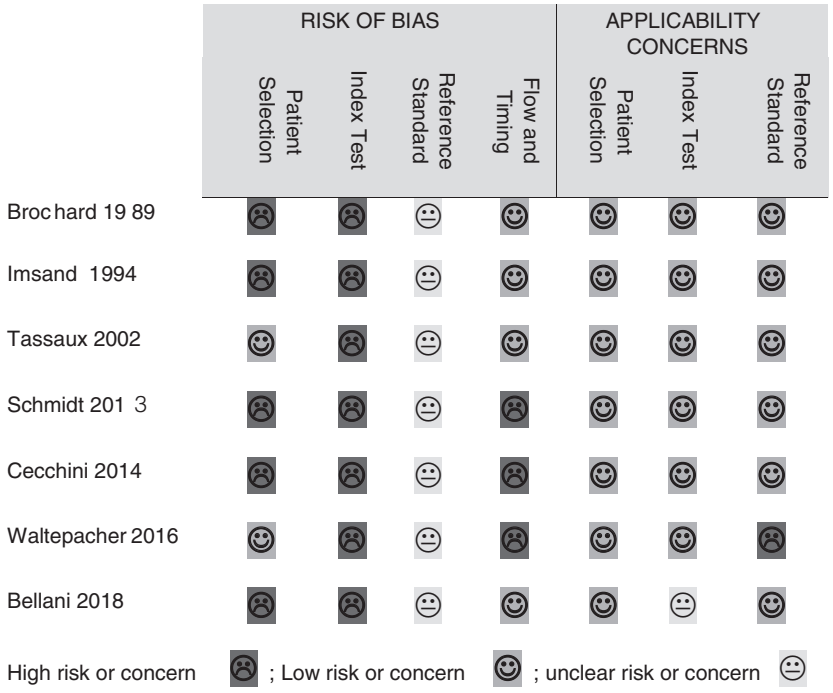


Figure 2 Quality Assessment of Risk of Bias & Applicability Concerns.

Mechanical loading/unloading of respiratory muscles

We evaluated the response of sEMG activity in each study and determined its responsiveness to of MV assistance based on changing ventilatory, mechanical, and neural output (increase, decrease, or no change). Of note, most of the studies did not report statistical correlation between sEMG and reference tests.

Activity of SCM,[31,32] parasternal,[17] scalene,[17,26] and ala-nasi,[17,26] muscles were responsive to the level of MV assistance reflected by the loading/unloading of respiratory muscles and its effect on RR, V_T,[17,26,31,32] $\dot{V}_E$, WOB (ΔPes -ΔV),[31] Pdi, Edi, H/L ratio of diaphragmatic EMG activity,[31] P_{ETCO_2},[26] $P_{0.1}$,[32] and the prevalence of ineffective triggering effort.[17] One study showed that sEMG activity of extra-diaphragmatic muscles was directly correlated with Edi ($r = 0.49$ to 0.71, $p < 0.0001$).[26]

SCM activity was similar between spontaneous and mandatory breaths during SIMV + PSV mode in one study, which was validated by constant WOB, $\dot{V}_E$, PTP and TI_e, $P_{0.1}$, EMG_{Ti}.[30] In contrast, while SCM activity matched constant ventilatory output during spontaneous and controlled breaths, its response was slow to the changes in ventilatory output across MV levels of assistance during PSV + SIMV mode.[30] However, the aggregate value for both SCM and Edi activity was responsive to change in WOB during high levels of MV assistance (sEMG activity decreased as MV support increased).[30]

Respiratory sensation

Only two of the seven included studies assessed respiratory sensation in which extra-diaphragmatic muscle activity was responsive to the level of dyspnea.[17,29] In one study, dyspnea was evaluated using VAS, which was directly correlated with EMG_{AUC} and EMG_{MAX} of parasternal, ala-nasi, and scalene muscles activity ($r = 0.72$ to 0.98, $p < 0.0001$).[5] The other study found that neither parasternal activity nor dyspnea level, measured using Borg scale changed with varying body positions, indicating a matched response between dyspnea and parasternal EMG measurements.[29]

Quality assessment

The QUADAS-2 tool was used to assess the quality of the included studies in terms of risk of bias and applicability concerns. Risk of bias was high in all 7 studies for the ''index test,'' 5 studies for ''patient selection,'' 3 for ''flow and timing,'' and the risk was unclear in all studies for the ''reference standard.'' Regarding applicability concerns, 1 study had unclear risk for the ''index test'', 1 study had high concern for the ''reference standard'', and all studies had low concern for ''patient selection'' (Fig. 2).

Discussion

This review was conducted to evaluate the quality of evidence available on using sEMG of extra-diaphragmatic muscles to assess respiratory responses during MV assistance. Data show that sEMG of extra-diaphragmatic muscles is regarded as a valid and applicable tool for assessing changes in mechanical loading/unloading of respiratory muscles and respiratory sensation during MV assistance. We found that the response of extra-diaphragmatic muscle activity measured via sEMG matched at least one of the respiratory responses summarized in this review (i.e., respiratory mechanical loading/unloading or respiratory

sensation) in all studies except for one study, which did not report sufficient data of extra-diaphragmatic muscles responses in their results.[28] However, the included studies lack the evidence of sEMG accuracy in assessing MV clinical outcomes (i.e., respiratory failure, MV liberation readiness, or success/failure). This is partly because these studies did not primarily use sEMG to determine its diagnostic accuracy and only used it as a research tool to show the effectiveness of various MV interventions.

The matching response of extra-diaphragmatic sEMG activity with the ventilatory output is due to the activation of these muscles as a compensatory response for increased ventilatory load and NRD, which are associated with weak diaphragm or under-assistance in patients with MV.[11,17,31] During the early phase of a failed MV liberation trial, patients display an increased mechanical load compared with those who had successful trial.[10] Extra-diaphragmatic muscle activity is increased to offset the declining ventilatory function,[11] which can explain the strong relationship between dyspnea and EMG activity of extra-diaphragmatic muscles in one of the included studies in this review.[17]

In light of this review's findings, the response of sEMG of extra-diaphragmatic muscle activation to MV assistance should be interpreted with caution. The mode of MV can be a confounding factor that interferes with the mechanical or neural output. For example, in one study the use of $\dot{V}_E$ was a weak parameter as a reference standard during ASV mode because it is pre-set to deliver a constant level of MV assistance.[32] Similarly, inspiratory neuromuscular output is pre-programmed for a given level of assistance and not based on a breath-by-breath basis during SIMV mode.[30] This explains the slow response of ventilatory parameters and SCM re-programming after a sustained change in ventilatory load in one study.[30] In addition, ventilatory compensation can be achieved by both RR and V_T to reach a constant $\dot{V}_E$ with the changing level of MV assistance.[17,30,32] One study reported an increase in RR but did not report V_T,[29] giving an incomplete picture of ventilatory output, since it could be interpreted as shallow breathing and not increased ventilatory efficiency as the study implies. Hence, extra-diaphragmatic sEMG activity should be considered with the reporting of both RR and V_T collectively as reference standards. Finally, posture should be taken into account as it can influence respiratory muscle activation.[33] Sitting position compared to supine and semi-recumbent positions reduced NRD to the diaphragm and not the parasternal muscle or dyspnea level during MV liberation trial.[29] Similarly, sitting position was found to require less activation of diaphragm and intercostal muscles compared to supine position with no effect on ventilatory output.[34]

The high risk of bias reported for patient selection is mainly related to the design of the studies in which random sampling was not performed or not reported (n = 4)[17,26,30,31] and for the exclusion of patients with COPD (n = 1).[28] The high risk of bias found in all of the studies for the ''index test'' is due to the fact that these studies did not use blinding of the researcher to the reference standards. This means that sEMG was interpreted with the prior knowledge of the reference standard results, which mainly represent instantaneous changes in ventilatory output during MV. Likewise, not blinding the researcher to the index test affected the quality of evidence for the ''reference standards.'' However, sEMG results often take time for processing which makes them less likely to generate bias in the instant results of the reference standards (ventilatory output). Hence, in addition to the lack of reporting of blinding, we evaluated the risk of bias for the reference standards to be unclear in all the studies.

High risk of bias for flow and timing in three studies was due to the exclusion of a total of 4 patients from the analysis in two studies due to the inability to record scalene sEMG[17,26] and one patient for the inability of measuring maximum inspiratory pressure (MIP).[29] Generally, there were few applicability concerns as the included studies matched most of the quality questions. The only high applicability concern was regarding the reference standard due to the incomplete information reported on respiratory mechanics in one study.[29] Also, unclear applicability concern of the index test was found in one study for the lack of sufficient reporting of sEMG of extra-diaphragmatic muscles.[28]

This review is limited by couple of factors that affect the quality of evidence of using sEMG of extra-diaphragmatic muscles as an assessment tool of respiratory responses during MV. The included studies had small sample sizes and, thus, the evidence of usefulness of this tool across a broad population of patients on MV is limited. Additionally, there is a lack of a systematic and well-designed approach for assessing sEMG diagnostic performance, which mainly includes: random sampling of patients, blinding to index test and reference standards, and the use of gold standard reference tests for assessing MV outcomes (i.e., rapid shallow breathing index (RSBI) and MIP).

Future directions: The findings of this review may stimulate further research to test the accuracy of sEMG as a clinical diagnostic technique, which might help in the decision making of MV liberation. Further studies addressing its diagnostic accuracy should aim to examine its performance in predicting MV outcomes such as MV liberation success/failure. Additionally, studies should investigate its cost and complexity in comparison with other standard methods of MV monitoring used in the critical care settings.

Conclusion

The use of sEMG of extra-diaphragmatic muscles appears to be a valid monitoring tool with low applicability concerns for assessing respiratory mechanical loading/unloading and respiratory sensation during MV. However, high risk of bias was associated with the identified studies in introducing this technique as an assessment tool. This quality flaw was mainly attributed to the fact that these studies were not primarily designed to evaluate sEMG diagnostic accuracy of MV monitoring.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authors contribution

- Both Mr. AbuNurah & Dr. Lowman contributed to the review search, data collection, study design, analysis of data, and manuscript preparation. Dr. Russell contributed to the manuscript preparation, review and editing.
- This study was performed at the Department of Physical Therapy, School of Health Professions, University of Alabama at Birmingham, Birmingham, Alabama.
- No potential conflict of interest relevant to this article was reported.
- King Saud bin Abdulaziz University for Health Sciences, KSA, supported Mr. AbuNurah's work on the present study.

References

1. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. New Engl J Med. 2008;358(13):1327–35.
2. Jaber S, Jung B, Matecki S, Petrof BJ. Clinical review: Ventilator-induced diaphragmatic dysfunction-human studies confirm animal model findings! Crit Care. 2011;15(1):206.
3. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med. 2018;197(2):204–13.
4. Goligher EC, Ferguson ND, Brochard LJ. Clinical challenges in mechanical ventilation. Lancet (London, England). 2016;387(10030):1856–66.
5. MacIntyre NR. Respiratory mechanics in the patient who is weaning from the ventilator. Respir Care. 2005;50(2):275–86, discussion 284-276.
6. Chiti L, Biondi G, Morelot-Panzini C, Raux M, Similowski T, Hug F. Scalene muscle activity during progressive inspiratory loading under pressure support ventilation in normal humans. Respir Physiol Neurobiol. 2008;164(3):441–8.
7. Jung JH, Kim NS. Relative activity of respiratory muscles during prescribed inspiratory muscle training in healthy people. J Phys Ther Sci. 2016;28(3):1046–9.
8. Perlovitch R, Gefen A, Elad D, Ratnovsky A, Kramer MR, Halpern P. Inspiratory muscles experience fatigue faster than the calf muscles during treadmill marching. Respir Physiol Neurobiol. 2007;156(1):61–8.
9. Ratnovsky A, Elad D, Halpern P. Mechanics of respiratory muscles. Respir Physiol Neurobiol. 2008;163(1-3):82–9.
10. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi Y-SA, et al. Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med. 2003;167(2):120–7.
11. Parthasarathy S, Jubran A, Laghi F, Tobin MJ. Sternomastoid, rib cage, and expiratory muscle activity during weaning failure. J Appl Physiol. 2007;103(1):140–7.
12. Dres M, Schmidt M, Ferre A, Mayaux J, Similowski T, Demoule A. Diaphragm electromyographic activity as a predictor of weaning failure. Intens Care Med. 2012;38(12):2017–25.
13. Yan S, Kaminski D, Sliwinski P. Inspiratory muscle mechanics of patients with chronic obstructive pulmonary disease during incremental exercise. Am J Respir Crit Care Med. 1997;156 3 Pt 1:807–13.
14. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. Nat Med. 1999;5(12):1433–6.
15. Beck J, Sinderby C, Lindstrom L, Grassino A. Influence of bipolar esophageal electrode positioning on measurements of human crural diaphragm electromyogram. J Appl Physiol (Bethesda, Md : 1985). 1996;81(3):1434–49.
16. Pillai JB, Vegas A, Brister S. Thoracic complications of nasogastric tube: review of safe practice. Interact Cardiovasc Thorac Surg. 2005;4(5):429–33.
17. Schmidt M, Kindler F, Gottfried SB, et al. Dyspnea and surface inspiratory electromyograms in mechanically ventilated patients. Intensive Care Med. 2013;39(8):1368–76.
18. Dos Reis IMM, Ohara DG, Januario LB, Basso-Vanelli RP, Oliveira AB, Jamami M. Surface electromyography in inspiratory muscles in adults and elderly individuals: A systematic review. J Electromyogr Kinesiol. 2019;44:139–55.
19. Kacmarek RM, Berra L, Villar J. On the road to surface monitoring of diaphragmatic activity in mechanically ventilated patients. Respir Care. 2018;63(11):1457–8.
20. Maarsingh EJ, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WM. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. J Appl Physiol (Bethesda, Md : 1985). 2000;88(6):1955–61.
21. Duiverman ML, Van Eykern LA, Vennik PW, Koëter GH, Maarsingh EJW, Wijkstra PJ. Reproducibility and responsiveness of a noninvasive EMG technique of the respiratory muscles in COPD patients and in healthy subjects. J Appl Physiol. 2004;96(5):1723–9.
22. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. Jama. 2009;302(21):2323–9.
23. Gandevia SC, McKenzie DK. Human diaphragmatic EMG: changes with lung volume and posture during supramaximal phrenic stimulation. J Appl Physiol (Bethesda, Md : 1985). 1986;60(4):1420–8.
24. Suh ES, Mandal S, Harding R, Ramsay M, Kamalanathan M, Henderson K, et al. Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD. Thorax. 2015;70(12):1123–30.
25. Zocchi L, Fitting J, Majani U, Fracchia C, Rampulla C, Grassino A. Effect of pressure and timing of contraction on human rib cage muscle fatigue. Am Rev Respir Dis. 1993;147(4):857–64.
26. Cecchini J, Schmidt M, Demoule A, Similowski T. Increased diaphragmatic contribution to inspiratory effort during neurally adjusted ventilatory assistance versus pressure support: an electromyographic study. Anesthesiology. 2014;121(5):1028–36.
27. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36.
28. Bellani G, Bronco A, Arrigoni Marocco S, Pozzi M, Sala V, Eronia N, et al. Measurement of diaphragmatic electrical activity by surface electromyography in intubated subjects and its relationship with inspiratory effort. Respir Care. 2018;63(11):1341–9.
29. Walterspacher S, Guckler J, Pietsch F, Walker DJ, Kabitz HJ, Dreher M. Activation of respiratory muscles during weaning from mechanical ventilation. J Crit Care. 2017;38:202–8.
30. Imsand C, Feihl F, Perret C, Fitting JW. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. Anesthesiology. 1994;80(1):13–22.
31. Brochard L, Harf A, Lorino H, Lemaire F. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis. 1989;139(2):513–21.

32. Tassaux D, Dalmas E, Gratadour P, Jolliet P. Patient-ventilator interactions during partial ventilatory support: a preliminary study comparing the effects of adaptive support ventilation with synchronized intermittent mandatory ventilation plus inspiratory pressure support. Crit Care Med. 2002;30(4): 801–7.
33. Segizbaeva MO, Pogodin MA, Aleksandrova NP. Effects of body positions on respiratory muscle activation during maximal inspiratory maneuvers. Adv Exp Med Biol. 2013;756:355–63.
34. Wanke T, Lahrmann H, Formanek D, Zwick H. Effect of posture on inspiratory muscle electromyogram response to hypercapnia. Eur J Appl Physiol Occup Physiol. 1992;64(3):266–71.

Pulmonol. 2020;**26(6)**:386–397

PULMONOLOGY

www.journalpulmonology.org

SPECIAL ARTICLE

Recommendations for interventional pulmonology during COVID-19 outbreak: a consensus statement from the Portuguese Pulmonology Society

F. Guedes[a,b,c,*], J.P. Boléo-Tomé[d], L.V. Rodrigues[e,f], H.N. Bastos[g,h,i], S. Campainha[j], M. de Santis[k], L. Mota[l], A. Bugalho[m,n]

[a] *Centro Hospitalar do Porto (CHP), Hospital Geral de Santo António (HGSA), Unidade de Broncologia, Serviço de Pneumologia, Porto, Portugal*
[b] *Departamento de Clínicas Veterinárias, Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), Universidade do Porto (UP), Porto, Portugal*
[c] *Centro de Estudos de Ciência Animal (CECA), Instituto de Ciências, Tecnologias e Agroambiente (ICETA) da Universidade do Porto, Praça Gomes Teixeira, Apartado 55142, 4051-401, Porto, Portugal*
[d] *Pulmonology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal*
[e] *Pulmonology Department, Hospital Sousa Martins, Unidade Local de Saúde da Guarda, Guarda, Portugal*
[f] *Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal*
[g] *Department of Pneumology, Centro Hospitalar São João, Porto, Portugal*
[h] *Faculty of Medicine, University of Porto, Porto, Portugal*
[i] *IBMC/i3S - Instituto de Biologia Molecular e Celular / Instituto de Investigação e Inovação em Saúde, University of Porto, Portugal*
[j] *Pulmonology Department, Vila Nova de Gaia-Espinho Hospital Center, Vila Nova de Gaia, Portugal*
[k] *Pulmonology Department, Instituto Português de Oncologia (IPO), Coimbra, Portugal*
[l] *Pulmonology Department, Hospital Pulido Valente, Centro Hospitalar Lisboa Norte, Lisboa, Portugal*
[m] *Pulmonology Department, CUF Infante Santo Hospital and CUF Descobertas Hospital, Lisbon, Portugal*
[n] *Comprehensive Health Research Centre, Chronic Diseases Research Center (CEDOC), NOVA Medical School, Lisbon, Portugal*

Received 24 June 2020; accepted 16 July 2020
Available online 5 August 2020

KEYWORDS
Interventional pulmonology;
Bronchoscopy;
Thoracocentesis;
COVID-19;
Consensus statement

Abstract Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by a novel SARS-CoV-2 pathogen. Its capacity for human-to-human transmission through respiratory droplets, coupled with a high-level of population mobility, has resulted in a rapid dissemination worldwide. Healthcare workers have been particularly exposed to the risk of infection and represent a significant proportion of COVID-19 cases in the worst affected regions of Europe.

Like other open airway procedures or aerosol-generating procedures, bronchoscopy poses a significant risk of spreading contaminated droplets, and medical workers must adapt the

* Corresponding author.
E-mail address: fernando.t.guedes@gmail.com (F. Guedes).

https://doi.org/10.1016/j.pulmoe.2020.07.007

procedures to ensure safety of both patients and staff. Several recommendation documents were published at the beginning of the pandemic, but as the situation evolves, our thoughts should not only focus on the present, but should also reflect on how we are going to deal with the presence of the virus in the community until there is a vaccine or specific treatment available. It is in this sense that this document aims to guide interventional pulmonology throughout this period, providing a set of recommendations on how to perform bronchoscopy or pleural procedures safely and efficiently.

Introduction

Coronavirus Disease 2019 (COVID-19), a new infectious disease that emerged in early December 2019 in Wuhan (China),[1] is triggered by a novel pathogen with phylogenetic similarity to what caused the severe acute respiratory syndrome (SARS) outbreak in 2003, and was called SARS-CoV-2.[2] Its capacity for human-to-human transmission and international air travel facilitated the rapid dissemination on an unprecedented scale to the rest of the world.[3,4]

In Italy, the latest figures reported that 9% of COVID-19 cases were health care workers (HCW), while in Spain the rate of medical staff infected reached 26%, the highest in Europe.[5] In Portugal, by 12th May 2020, 11.3% of infections occurred in HCW.[6] There are at least two explanations for such a high number of infected personnel. First, the lack of proper personal protective equipment (PPE) at the beginning of the epidemic, when assisting both confirmed and suspected patients with COVID-19. Second, the duration of exposure to infected patients undergoing aerosol-generating procedures, such as non-invasive ventilation (NIV) and bronchoscopy, directly resulting in a significant increase in the risk of transmission to HCW.

The Portuguese Society of Pulmonology recently issued a set of recommendations for bronchoscopic procedures,[7] shortly after the diagnosis of the first cases in Portugal. The document aimed to guarantee the protection of both patients and medical practicioners, and to ensure that the healthcare workforce would be conserved to fullfill their mission throughout the period. Since then, a significant amount of scientific evidence has been accumulated; so, the present document gives an update of the available literature, providing practical suggestions for pulmonologists undergoing bronchoscopy or pleural procedures in the setting of the current and post-pandemic phases.

Risk of transmission

Respiratory droplets comprise the main route of SARS-CoV-2 transmission, although airborne transmission is also possible through aerosol-generating procedures, such as bronchoscopy.[8] One study during the H1N1 pandemic provided experimental evidence that bronchoscopic procedures increases more than 4 times the viral copy number per litre in positive air samples.[9] While the heavy droplets rapidly settle, aerosol particles are much smaller (<5—10 μm) and are dispersed in the air over extensive distances, posing a considerable risk of infection in enclosed spaces, specially if poorly ventilated.[10]

The contribution of asymptomatic carriers has also been subject of debate.[11,12] A significant proportion of them have lung abnormalities on chest CT scans[13,14] and a high level of viral shedding may be detected in presymptomatic patients,[14] so it is likely that transmission occurs in the early stages of infection when patients are either minimally symptomatic or asymptomatic. Unrecognized patients pose a real challenge to infection control and, when not promptly handled with appropriate airborne precautions, are one of the most critical factors for SARS-CoV-2 infection spread in the healthcare setting.

Methods

The Portuguese Pulmonology Society appointed FG to chair this consensus group. Seven national IP specialists were selected based on their clinical expertise and different settings (university vs. non-university hospitals; state vs. private hospitals; pulmonologists vs. critical care specialists; ...). At the first online consensus meeting, attended by all members, a primary draft with several sections was created. This was shared online and further improved by written comments and suggestions. Then, each IP specialist was assigned a specific section presented in this document and was responsible for reviewing and evaluating the relevant available literature related to the topic. Electronic databases (Pubmed, OVID Medline and Embase, Web of Science, Cochrane Central Register of Controlled Trials) were used to search for the terms ''COVID-19'' OR ''SARS-CoV-2'' AND (''bronchoscopy'' OR ''interventional pulmology'' OR ''thoracentesis'' OR ''thoracocentesis'' OR ''pleural effusion'' OR ''pneumothorax'' OR ''rigid bronchoscopy'' OR ''thoracoscopy'' OR ''chest drain''). Position papers from major health organizations (US Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control and World Health Organization) and important scientific societies (European Respiratory Society, European Association for Bronchology and Interventional Pulmonology, American Association for Bronchology and Interventional Pulmonology, World Association for Bronchology and Interventional Pulmonology and British Thoracic Society) were also reviewed.

In a second online conference the complete draft was evaluted by all team members and two working groups were created. They were responsible for discussing and revising different sections, and editing the text for consistency. Afterwards, the final manuscript was distributed to the consensus group members and assessed for final approval.

Adaptations of the interventional pulmonology (IP) department

Although there is still some heterogeneity in the definition and scope of of ''interventional pulmonology'' (IP), it has become the most widely accepted term to describe the use of techniques for the diagnosis and treatment of a growing number of thoracic disorders.[15]

In the context of this document, the term IP is used to encompass the concepts of bronchoscopy (diagnostic or therapeutic), advanced bronchoscopy (flexible or rigid bronchoscopy and all its associated techniques), pleuroscopy (rigid or semi-flexible) and other simpler pleural techniques (such as thoracentesis, placement of thoracic drainage systems and indwelling pleural catheters). Though we acknowledge this wider definition of IP may be controversial, it covers all technical domains that most Portuguese pulmonologists need to address, and for the purpose of this document, it positions us to issue general recommendations. In the following subsections, specific scenarios of different technical specializations will be addressed in order to overcome this broader definition and to apply it better to individual settings.

The IP department is a high-risk area, given the type of procedures that are performed with airway manipulation and with multiple staff involved. Although this setting is generally designed to deal with occasional airborne infectious diseases, such as tuberculosis, it is not prepared to systematically assess high-risk cases that need additional resources, diminish productivity and effectiveness and generate a huge workload.

Thus, each IP unit must rethink their administrative and logistic circuits in different areas, as well as the type and timing of performed procedures, to protect both HCW and patients. Moreover, as international health associations advocate, an infection-control program in healthcare settings should be implemented, consisting of a three-level hierarchy, including administrative, environmental and engineering controls, and personal protection equipment (PPE).[16] In the following subsections, each of the above listed hierachic levels are briefly presented.

Administrative and organizational issues

Administrative and logistic measures are crucial to ensuring safety while still maintaining IP activity.[17] Some general precautions include:

- All referrals and requests to the IP unit must preferably be made by telephone or digital means.
- Upon schedule and 24—48 h prior to arrival at the IP Unit, patients should be contacted by telephone and submitted to a pre-screening checklist that includes questions about 1) recent symptoms suggestive of COVID-19 (e.g. fever, cough, chills, muscle pain, shortness of breath/difficulty breathing, headache, sore throat, loss of taste or smell); 2) contact with suspicious/confirmed SARS-CoV-2 cases; and 3) occupational exposure.
- Patients who have recent respiratory and infectious symptoms and/or chest imaging suggestive of COVID-19, should have their elective procedures postponed and rescheduled after all symptoms are resolved.
- On arrival at the IP Unit, all patients must be asked again for respiratory symptoms and have their temperature checked.
- If possible, all patients should have at least one negative RT-PCR for SARS-CoV-2 in the 24—48 h preceding the exam. In patients with a positive RT-PCR SARS-CoV-2, the decision to procede with the intervention will be based on the urgency of the procedure (Chart 1 and Table 1).
- The IP unit should keep a record of deferred patients to reschedule their procedures according to the COVID-19 outbreak situation, as proposed in Table 2.

Environmental and engineering control

Physical space preparation

The design of strategies to minimize risks and a protocol fitting the characteristics of each specific Unit are crucial.[18]

- Reception, administrative, clinical and waiting areas should separate confirmed/high-risk patients from negative/low-risk ones. In addition, inpatients should be segregated from outpatients, either by time or physical location, to prevent cross infection.
- Specific circuits and written workflow plans must be prepared, covering the pre-procedural area, procedural room, post-procedural area, decontamination and reprocessing. The implementation of a flowchart with different areas and walking paths using a visual colour zone system can be useful: 1) red zone for contaminated areas; 2) yellow zone for transition areas, and 3) green zone for non-COVID-19 safe areas[19] (Fig. 1A). These need to be formulated by internal elements from the IP unit with the cooperation of a multidisciplinary team of hospital members, including administration, engineers, and infection control board.
- A specific place to store and retrieve all items required for PPE should be defined inside the Unit.
- A designated area in the Unit should be selected, close to the procedural suite, for gowning and removal of all PPE, according to hospital protocol and standards, in order to reduce exposure to contaminated particles and droplets. When an anteroom is available, it may be used as an area for donning and doffing of PPE (Fig. 1B).
- Stations should be created to facilitate frequent hand hygiene and to distribute waste containers according to local infectious control recommendations. Posters and other visual aids should be placed at strategic locations around the intervention suite to act as reminders.
- Emergency procedures in COVID-19 positive patients should preferably be performed within the ICU enviroment, with controlled airway through cuffed endotracheal tube and assisted ventilation.

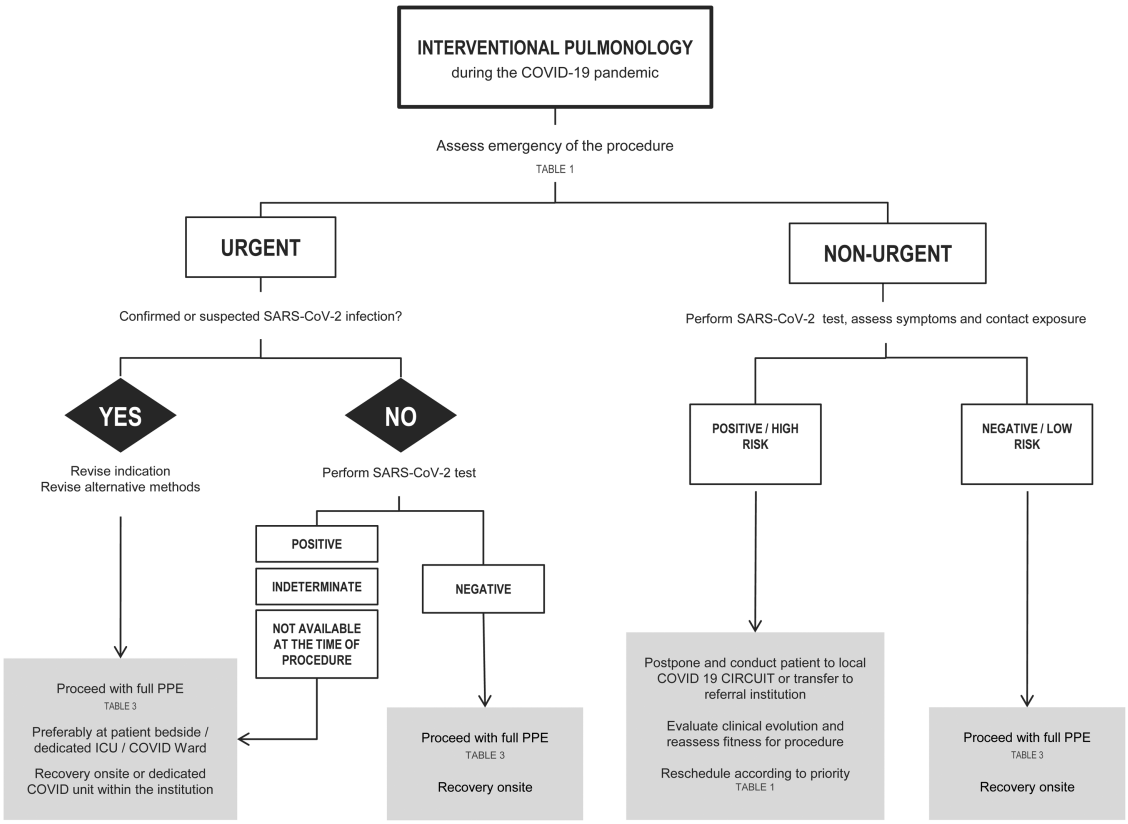


Chart 1 Proposed triage of IP procedures during the COVID-19 outbreak.

Table 1 Priorization of IP exams according to SARS-CoV-2 status and procedure urgency.

	URGENT PROCEDURES	NON-URGENT PROCEDURES	
		NON-DELAYABLE (<2-4 weeks)	DELAYABLE (≥4 weeks)
COVID-19 NEGATIVE/POSITIVE	Massive hemoptysis with airway compromise Acute foreign body aspiration Severe symptomatic central airway obstruction Suspicion of alternative (non-COVID-19) acute and severe infectious disease Airway management in difficult and non-delayable endotracheal intubation or complicated percutaneous tracheotomy Large and symptomatic pleural occupation (air, fluid, blood, pus)		
COVID-19 POSITIVE/HIGH RISK	Removal of copious secretions and mucus plugs Possibility of superinfection (community acquired or nosocomial) Severe suspicious cases of COVID-19 that need to be confirmed by bronchoscopy and minimal bronchoalveolar lavage, after at least 2 negative/inconclusive naso-pharyngeal RT-PCR SARS-CoV-2 tests		
COVID-19 NEGATIVE/LOW RISK		Lung cancer diagnosis and staging Increased mediastinal and/or hilar lymph nodes Suspected pulmonary infection in immunosuppressed hosts Suspicion of pulmonary tuberculosis (after negative sputum) Interstitial lung disease in symptomatic and lung function deteriorating patient s Mild-to-moderate airway stenosis Mild persistent hemoptysis Pleurodesis or indwelling pleural catheter placement for recurrent and symptomatic pleural effusion	Routine evaluation of tracheobronchial stenosis or endobronchial stent Surveillance of lung transplant patients Mild asymptomatic benign airway stenosis Minor pulmonary CT abnormalities in an asymptomatic patient Chronic cough evaluation (without chest CT or lung function abnormalities) Interstitial lung disease differential diagnosis in non-symptomatic or non-deteriorating patients Bronchoscopic lung volume reduction Bronchial thermoplasty Minimal pleural effusion in asymptomatic patients

Table 2 Schedule of IP procedures according to the stage of COVID-19 pandemic.

COVID-19 in the community	IP Unit
Exponential increase of new cases	Urgent cases – only
Rapid increase of new cases	Urgent cases – only Elective but not delayable – evaluate case-by-case
Decrease in new cases	Urgent cases – full capacity Elective, but not delayable – full capacity Elective and delayable – resume partial capacity
Absence of new cases in the last 2 weeks	Resume all cases with full capacity

- Elective procedures should be reserved for COVID-19 negative patients (Chart 1 and Table 1). Nevertheless, these procedures should still be performed in a dedicated negative pressure room (see below, ventilation requirement) with strict isolation precautions and sufficient ventilation to avoid aerosol contamination.[20] If these requirements are not met in the bronchoscopy suite, then in a different venue, such as an operating theatre, isolation room or the ICU with negative pressure, if available.
- If negative pressure rooms are unavailable througout the instituition, a specific and dedicated room with adequate natural ventilation (see requirement below) may be an alternative, provided that appropriate intervals between procedures are reserved and that the suspected COVID-19 cases be programmed after all planned non-COVID daily activity, so that the unit can be carefully cleaned (following the disinfection policy) and ventilated.
- Keep the endoscopy room for procedures only (all other activities, such as planning, reporting and laboratory requisition should take place elsewhere).
- Suspected and confirmed cases of COVID-19 must be placed in an airborne infection isolation room with negative pressure before and after the procedure. Low-risk and negative patients can remain in the pre-procedural and recovery area, if there is adequate room ventilation, protective equipment (e.g. surgical mask) and physical distance (>2 m) from other negative patients.

Ventilation

- Patient source control strategies, such as wearing a mask should be encouraged.
- Whenever feasible, it is recommended procedures are pereformed in a room that meets the ventilation requirements for Airborne Infection Isolation (AII), ensuring the dilution and removal of contaminated air. The preferred system is a negative pressure room with at least 12 air changes per hour (ACH) with airflow direction control (single-pass or recirculation systems with HEPA filtration). Alternatively, natural ventilation with an airflow of at least 160 L/s is an option.[19,21]
- Enough time should be allowed to ensure that contaminated air is removed from the room before performing another procedure in the same room (depending on ACH and disinfection methods, but at least 30 min). Local adaptations must be considered according to the characteristics of the IP unit.

Cleaning and disinfecting patient care equipment and rooms

Endoscopes are considered semi-critical medical instruments according to the Spaulding classification.[22] Recommendations from the Centers for Disease Control and Prevention (CDC) on reprocessing procedures should be followed. These include pre-cleaning, leak-testing, manual cleaning and visual inspection followed by disinfection/sterilization.

- A high-level manual disinfection or using an automated endoscope reprocessor is recommended.
- Proper storage and documentation are also an integral part of the reprocessing workflow.
- A pathway of contaminated equipment must be defined, as well as adequate packaging to minimize exposure (for example, a hermetic box).
- If available, disposable bronchoscopes are recommended for confirmed COVID-19 patients with clear advantages in

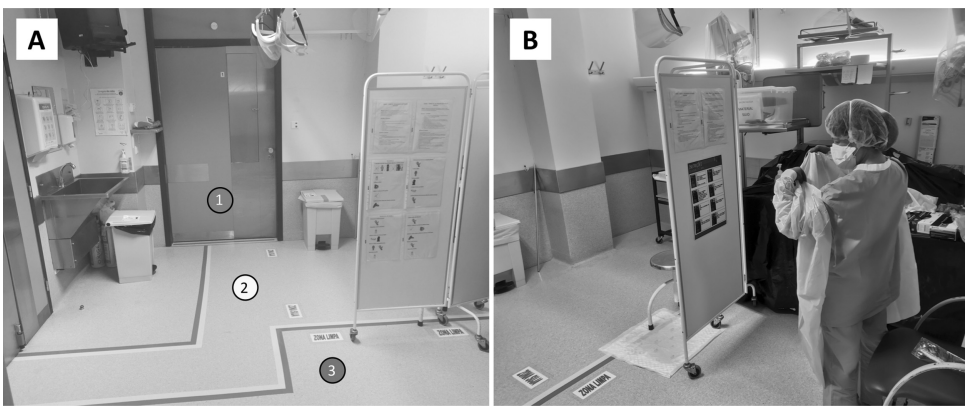


Figure 1 A. Implementation of specific circuits with colour visual zone system to distinguish contaminated (1, red zone), transition (2, yellow zone) and safe cleaned areas (3, green zone). B. Designated area for donning and doffing of PPE, where posters and other visual aids were placed strategically to act as reminders.

Table 3 Specifications for personal protective equipment during IP procedures.

PPE	Characteristics/specifications/standards	Observations
Gloves	◯ Single-use ◯ Waterproof ◯ Standard EN ISO 374-2:2014, 374-3:2014 e 374.5:2016 ◯ Double gloves: - first: long sleeved gloves - second: nitrile gloves	
Eye Protection	◯ Goggles with lateral protection ◯ Face shield	If not for single use, perform disinfection with ethanol base solution or 0.1% sodium hipochlorite
Gowns	◯ Single-use ◯ Waterproof ◯ Long sleeved ◯ Standard EN 14605:2009	Consider biological risk protection EN 14126:2004, if confirmed positive patient
Cap	◯ Single-use	Consider hood cap, if confirmed positive patient
Shoe cover	◯ Single-use	
Respiratory Protection	◯ FFP2/N95	Perform seal check before enter the endoscopy suite.
	◯ Single-use	Consider FFP3, if confirmed positive patient

PPE, personal protective equipment.

portability, post-procedural handling and cross contamination risk.[23]
- Floors and surfaces of the endoscopy suite must be disinfected after each procedure.
- Intermediate level disinfectants with proven activity against enveloped viruses include 0.1% sodium hipochlorite, 62–71% ethanol, 0.5% hydrogen peroxide and quaternary ammonium compounds.[19,24,25]

Personal protective equipment

IP procedures are considered to be consistently subjected to the highest risk of exposure. In this setting, full precautions must be taken to cover all different possible types of transmission (contact, droplet and airborne).[26] Personnel involved in the reprocessing procedure must also wear protective equipment consisting of eye protection, respiratory mask FP2, long sleeved gown and double gloves.[27,28] The recommendations for the use of PPE are shown in Table 3.

Specimen transportation

Samples from the upper and lower respiratory tract, including pleural effusion, are deemed to be the most potentially infectious. Consequently, they should be handled as Category 3 pathogen and double-bagged (first the specimen must be bagged in the patient's room and then taken out of the room and placed in a separate pre-labeled specimen bag). All specimens must be manually delivered.[28,29]

Safety rules for staff and patients

It is also important to define proper new rules for both HCW and patients circulating in the IP unit, as listed below:

Health professionals

- The IP Unit should reduce and prioritise the allocation of human resources according to the outbreak evolution and hospital needs. The minimum number of staff required to ensure a correct operation must be clearly defined.
- It is essential that all personnel follow, train and maintain competency in effective hand hygiene and every aspect of PPE (theoretical, training and simulation sessions) so that everyone is familiar with their role.
- All interactions with patients, including informed consent, should be done with appropriate PPE and frequent hand washing. The staff should not reduce the level of awareness and protection, and the idea that patients with suspected COVID-19 should be handled in the same manner as confirmed cases must be reinforced.
- A core team that includes only essential HCW should perform the procedure on SARS-CoV-2 positive patients. The most experienced staff should be responsible for the exam to reduce time and deal effectively with possible complications. Other healthcare personnel, such as residents, medical students and visitors should not be inside the unit and the examination room before, during or after the procedure.
- Of note, the scheduled exams must be done during normal working hours (avoiding an emergency basis or setting) and in an appropriate, designated room that fulfils all the standards required for care.

Patients and other personel

- Respiratory and contact isolation should be standard and mandatory for all patients. Outpatients and inpatients should always enter the IP Unit with a suitable face mask and keep it on at all times (until the beginning and after the end of the procedure) to minimize the risk of transmission. No unnecessary personal items should be brought into the IP unit.
- Family members and caregivers should not stay in the IP waiting rooms. In case of children or patients in need of support, the Unit can allow a single relative to enter the preparation area to provide aid.
- The entry into the Unit of suppliers and medical devices sales representatives must be restricted.

Prioritization of procedures

Scheduled elective procedures should be reviewed and cancelled if potentially delayable, until local control of the outbreak is achieved. After flattening the infectious curve, many elective IP procedures will have to be performed, as they are essential to provide a definitive diagnosis and effective treatment. At this time, it is advisable to evaluate the delayed requests and to optimize the procedure planning based on clinical needs and operational capability.

A suggested rational approach for stratification of procedures is provided in Table 1, but we recognize that, in certain cases, the indication may not be straightforward, and the risk-benefit must be weighted on an individual basis by the IP team.[31] Although rescheduling certain procedures is obvious in other cases it may not be desirable or ethical. It is important to note that these indications may change according to local epidemiological conditions and the response capabilities of the healthcare system. Several societies have recommended different levels of procedure stratification.[26,30,31] Briefly, what is recommended is a stepwise reopening of elective IP procedures according to the national and local COVID-19 outbreak situation, depending on the number of new confirmed cases, hospital admitted cases (ward and ICU), availability of equipment and healthcare staff, time elapse and number of postponed IP cases. Some authors[34] have proposed a summary of the elective endoscopic procedure by phases, as shown in Table 2. Anyway, it should be noted that the evolving procedural criteria should always be communicated to other physicians who refer patients for invasive respiratory procedures and to the hospital administration.

Recommendations for bronchoscopy

Bronchoscopy under spontaneous ventilation

The following reccomendations are expert opinion-based and should be adapted to local regulations and guidelines. In an optimal scenario, it is safer to perform elective bronchoscopy under general anesthesia and orotracheal intubation, clinical conditions permitting. If this is not possible, bronchoscopy can be performed under spontaneous ventilation. Some recommendations are listed below:

- Operator should be standing behind the patient's head to reduce direct exposure. Oxygen supplementation should be done without the use of humidification, either through a nasal cannula or preferably with an oxygen mask with an entrance to the bronchoscope (Fig. 2A).
- For flexible bronchoscopy, a transnasal approach should be preferred, and a surgical mask should be placed over the patient's mouth to minimize droplet emission (Fig. 2B).
- In hypoxemic patients, bronchoscopy can be performed under NIV, using a closed circuit ventilation (double circuit with viral filters in both arms) and non-ventilated masks with a dedicated bronchoscope entrance (Fig. 2C). High performance NIV ventilators with FiO_2 regulation are preferable. From the end of the procedure, NIV should be continued for 1−2 h, titrating the FiO_2 to obtain an SpO_2 of around 94–95%.
- Bronchoscopy under nasal high-flow oxygen therapy is not reccomended and thus should be avoided.
- Nebulized medications should be avoided before or after the procedure.
- Proper sedation should be used to minimize cough reflex and to increase patient cooperation.
- An oral aspiration cannula should be available during the procedure (Fig. 2B).
- A transparent protective box may enhance safety by containing dispersal of droplet particles (Fig. 2D). The box is placed over the patient's head prior to bronchoscopy, with the anesthesia equipment already in place. The bronchoscope is inserted through the covered opening behind the patient (Fig. 2E).

Bronchoscopy in the intubated patient

The following recommendations are directed for patients under mechanical ventilation in an ICU setting due to respiratory failure. As reported, 5% of COVID-19 patients can develop respiratory failure and will need ventilatory support[32]; moreover, associated bacterial, viral and fungal co-infection should not be negleted.[33] In critically ill patients under invasive ventilation, ventilator-associated pneumonia occurs in up to 30% and lobar collapse is frequent and multifactorial.[34] The same adaptations apply to elective procedures under general anesthesia, performed in the Bronchoscopy Unit or Operating Theatre.

- A cuffed endotracheal tube is preferred over supraglotic devices, such as a laryngeal mask; cuff pressure should be maintained between 25–30 cmH_2O.[35]
- General anesthesia with muscle relaxant is recommended to reduce the aerosol production.
- FiO_2 should be adjusted to 100%.
- Volume control, pressure-limited mode is preferable and PEEP should be kept at the same level during the procedure. Adjustments can be made dynamically, with a prior assessment of the anticipated risks (e.g., lung derecruitment and desaturation, arrhythmias, pneumothorax).
- To avoid aerosol dispersion, a simple and appropriate maneuver consists of clamping the ventilation circuit just before introduction of bronchoscope, repeating the same step just before withdrawal.

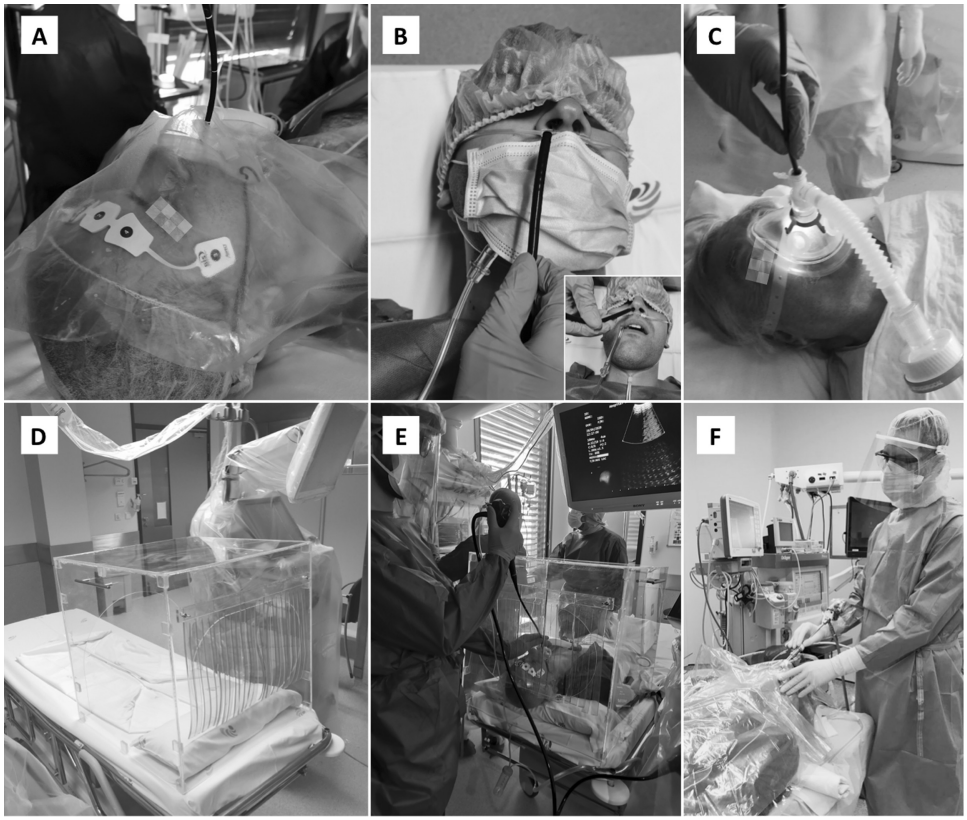


Figure 2 Strategies to minimize droplets dispersal during bronchoscopy. A. The bronchoscope may be introduced through an opening made at the oxygen mask, in this case with an additional plastic sheet covering the patient's head. B. Transnasal approach, with oxygen supplementation through nasal cannula and a surgical mask placed over the patient's mouth and the oral aspiration canulla. C. Bronchoscopy can be performed under ventilatory support, using a closed circuit ventilation and non-ventilated masks with a dedicated bronchoscope entrance. D. Transparent protective box may contain droplet particles inside. E. Protective box placed over the patient's head during endobronchial ultrasound. F. Rigid bronchoscopy with rubber caps on the ports of the scope and a plastic covering.

- Bronchoscope removal and reinsertion should be avoided during the procedure.
- In hypoxemic patients, if bronchoalveolar lavage is needed for diagnostic purposes, the volume used should be reduced to a minimum. If a SARS-Cov-2 diagnosis is needed, a minimum of 2—3 mL of recovered lavage is enough.[26]

Rigid bronchoscopy

Rigid bronchoscopy is used for diagnostic and therapeutic purposes, in procedures where flexible bronchoscopy would be deemed difficult or even impossible, like obtaining larger samples of endobronchial lesions, foreign body removal, management of central airway obstruction (including ablative techniques, like electrocautery, argon plasma coagulation, laser, cryotherapy, among others, and placement of airway stents) or massive hemoptysis.[36]

There are different ventilation strategies used during rigid bronchoscopy, although manual jet ventilation and high frequency jet ventilation are much the most frequent.[37] Common to these two techniques is the fact that the proximal end of the bronchoscope is open to allow the passage of instruments, thus ventilation is achieved providing 100% oxygen under high pressure (usually 50 psi) through an open system.[39,40] The use of these ventilation techniques means that aerosols are released into the room, making it a high-risk procedure.

In patients with suspected or confirmed COVID-19 diagnosis, rigid bronchoscopy should be avoided, except for urgent cases (Table 1). Clinical scenarios are mostly therapeutic, like acute foreign body aspiration, massive hemoptysis (when there is no place for embolization), severe symptomatic central airway obstruction (either benign or malignant) and migrated stents. In a clinically stable patient, upon suspicion of foreign body aspiration, one should consider non-contrast computerized tomography (CT) to confirm the presence of a foreign body before rigid bronchoscopy, to avoid unnecessary exams.[38,39]

In some centers, the rigid scope is used to perform other techniques, like Endobronchial Ultrasound-Transbronchial Needle Aspiration (EBUS-TBNA) or transbronchial cryobiopsy; this provides comfort to the operator and safety in case of major bleeding. The authors recommend performing these diagnostic procedures through cuffed endotracheal tube to minimize the risk of exposure. However, the operator must be ready to convert to rigid bronchoscopy, if necessary.

In a patient undergoing rigid bronchoscopy, it is recommended that:

- Rigid bronchoscopy should always be performed in a negative pressure room.
- Controlled ventilation is preferred, with the rigid bronchoscope used like an endotracheal tube.
- Air leaks should be reduced using rubber caps on the ports of the rigid scope, as well as using a plastic covering (Fig. 2F) or filling the mouth with gauze.[40] While this strategy is more appealing to minimize aerosol spread, the operator may find it challenging to handle instruments through the working channel.

Recommendations for pleural techniques

Pleural effusion does not appear to be a prominent feature of COVID-19. It occurs in 5.3–5.8% of patients, according to two recent meta-analyses.[41,42] There have been occasional reports of bilateral effusion that resolved spontaneously.[43] As bacterial superinfection is common in severe patients, they can also develop complicated effusions or empyema, requiring targeted treatment. There have been a few anecdotal reports of spontaneous pneumothorax and pneumomediastinum in severe COVID-19 pneumonia, requiring drainage.[44,45] This may be more frequent in critical patients on invasive ventilation, which can lead to bronchopleural fistulae.[46] It is, therefore, plausible that pleural drainage may be necessary in some COVID-19 patients, either in the ICU or in the ward, and indications for drainage do not differ from the standard clinical guidelines. However, as with any invasive procedure in confirmed COVID-19 patients, all precautions regarding the full use of protective equipment should be taken. The procedure must be performed by trained and dedicated staff to reduce its duration and to minimize the risk of complications. In other situations, the use of ultrasound may be very helpful with COVID-19 patients.[47] Besides its wide availability, safety and low cost, it is easy to use at the bedside and allows medical staff to detect small pleural effusions and to guide pleural fluid collection and drainage, if needed. On the other hand, even patients without suspected COVID-19 can have assymptomatic infection; so, any procedure should be considered as a possible COVID-19 case and precautions should be taken. Indeed, although some procedures may be postponed, in many situations they should not be deferred, especially in suspected or confirmed cancer patients. It is crucial that cancer patients do not experience delays in diagnostic or therapeutic procedures due to the present contingency.[48]

Few societies have published guidelines addressing pleural procedures during COVID-19 pandemic. The British Thoracic Society has issued guidance on pleural services provision,[49] mainly to minimize hospital visits and admissions and to ensure both patient and staff safety. Nonetheless, although we recognize lack of published evidence supporting these reccomendations, this document will adopt some of them.

First of all, despite pleural procedures not being listed as Aerosol Generating Procedure (AGP) in the CDC updated reccomendations,[50] they should be considered so and Level 2 PPE should be worn, as described above. Other societies have considered potential AGP as any procedure *''likely to induce coughing, that should be performed cautiously and avoided if possible''*.[51] This is particularly relevant to open procedures, such as thoracoscopy and indwelling pleural catheter insertion, and in case of pneumothorax with suspected bronchial-pleural fistula. Thus, we recommend taking the following precautions:

Pleural effusion

- On suspicion of malignant effusion, diagnostic pleural fluid aspiration should be performed, especially if the patient is a candidate for systemic therapy or if the effusion is symptomatic (Table 1).
- Consider placement of indwelling pleural catheters for recurrent malignant pleural effusions, avoiding repeated hospital drainage or admission.
- On suspicion of pleural infection, pleural fluid aspiration and analysis should be performed.
- In case of benign pleural effusions, the risk-benefit should be discussed with the attending physician; procedures can be postponed if the patient is not symptomatic.
- Thoracoscopy is not recommended as a principle; however, in the absence of alternative options, its risk-benefit must be assessed.

Pneumothorax

- Spontaneous primary pneumothorax can be managed in outpatient care if the risk assessment allows and if there is local team experience; needle aspiration and discharge should be considered if the patient is minimally symptomatic.
- When pleural drainage placement is necessary, if there is local expertise and the patient is at low risk, the use of pleural vent systems should be considered, thus allowing the patient to be managed at home.

Chest drainage placement and care

- Extra care must be taken when placing the chest tubes, in order to avoid open communication with the pleural space and the potentialemission of droplets and aerossols.
- When chest tubes are placed in ventilated patients, consideration should be given to clamping the ventilator circuit before assessing the pleural cavity, so that positive pressure spreading of pleural air or fluid can be prevented.
- Whenever possible, the use of non-wired pleural drainage should be considered; it can be connected to the drainage system before insertion into the pleural cavity (closed circuit).
- When pleuroscopy is required, the use of one way valve trocars should be preferred to assess the pleural cavity and properly seal the entrance port of the pleuroscope.
- In case of prolonged air-leaks, the use of wall suction should be weighted to create a closed system.

Table 4 IP Unit checklist during COVID-19 outbreak.

PRE-PROCEDURE PLANNING	PROCEDURE EXECUTION	POST-PROCEDURE
Adapt the IP unit to include: ✓ Preprocedural area ✓ Procedural room with negative pressure or adequate ventilation[1] ✓ Postprocedural area for decontamination, reprocessing and removal of PPE	**Gown adequate PPE** (Table 3) **and perform procedure at adequate endoscopy suite**[1]	**Collect respiratory samples** (including pleural fluid) **in closed circuits and double-bag for transport**
Revise prioritization of all procedures (table x and x)	**Minimize direct exposure** ✓ Stand behind the patient's head ✓ Place surgical mask over the patient's mouth ✓ Adapt oral aspiration cannula ✓ Avoid humidified O2 and nebulized drugs ✓ Use appropriate sedation	**If available, use disposable bronchoscopes for confirmed positive / highly suspicious COVID-19 patients**
Perform telephone pre-screening check-list (upon schedule and 24-48h before the exam) [2] ❑ Symptoms ❑ Contact history ❑ Occupational exposure	**In ventilated patients:** ✓ Prefer cuffed endotracheal tubes over supraglottic devices ✓ Clamp the ventilation circuit when removing or inserting the bronchoscope and immediately before assessing the pleural cavity when placing pleural drainages	**Reprocessing of bronchoscopes must be considered an AGP** ✓ Gown adequate PPE (Table 3) ✓ Perform procedure at adequate unit[1]
Test for SARS-CoV-2 in the 24-48h preceding the exam	**Avoid rigid bronchoscopy** (except if indicated for urgent purposes)	**Disinfect floor and surfaces of the endoscopy suite after each procedure**
Proceed according to priority / test result / risk probability (Flowchart 1, Table 1)	**Avoid thoracoscopy** (except if lack of alternative and after adequate risk/benefit stratification)	**Allow adequate time (>30min) to elapse before next procedure**
	Reduce teams and time of the procedure to minimal necessary	**Perform sequential removal of PPE and adequate hand hygiene**

1. The preferred system is a negative pressure room with at least 12 air changes per hour with controlled of airflow direction (single pass or recirculation systems with HEPA filtration). Alternatively, natural ventilation with an airflow of at least 160 L/s is an option.
2. Pre-screening checklist should include questions regarding (1) recent symptoms suggestive of COVID-19 (namely fever, cough, shortness of breath/difficulty breathing, chills, muscle pain, headache, sore throat, loss of taste or smell), (2) contact with suspicious or confirmed SARS-CoV-2 cases, (3) occupational exposure, and (4) recent travel history to a high-incidence region

AGP: Aerosol generating procedures. PPE: personal protective equipment. IP: Interventional Pulmonology.

Concluding remarks

As with other societal consensus papers, this document was developed by a restricted panel of experts from the Portuguese Society of Pulmonology; individual clinical judgment and local resources may lead to alternative perspectives. This guidance was based on the current knowledge of COVID-19, but, as new data appears, this statement should be revised in the future to accommodate updated recommendations. At present, one of the controversial assumptions is that, every patient, even if asymptomatic, should be assumed as potentially infected with SARS-CoV-2. Therefore, it is mandatory that contact precautions and proper training on donning and doffing of PPE be provided to all HCWs involved in IP. Another key element is to plan in advance and keep each IP Unit well-organized (Table 4). Although the reduction in the number of elective procedures represents one of the central strategies to improve safety, it is crucial that patients do not suffer unnecessary delays in diagnostic or therapeutic procedures due to the current contingency. Taken together, our ultimate intention is to bring full attention to this and future outbreaks or other emerging medical situations.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506, http://dx.doi.org/10.1016/S0140-6736(20)30183-5.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33.
3. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565–74.
4. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report 99; 2020.
5. European Center for Disease Prevention and Control. Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update, 8 April 2020. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-coronavirus-disease-2019-eighth-update-8-april-2020.pdf (accessed on 15th June 2020).
6. https://covid19.min-saude.pt/ (accessed 15th June 2020).
7. https://www.sppneumologia.pt/uploads/subcanais2_conteudos_ficheiros/posicao-da-spp-para-a-realizacao-de-broncoscopias-durante-a-pandemia-do-coronavirus-(2).pdf (accessed on 15th June 2020).
8. Wilson NM, Norton A, Young FP, Collins DW. Airborne transmission of severe acute respiratory syndrome coronavirus-2 to healthcare workers: a narrative review. Anaesthesia. 2020;(April), http://dx.doi.org/10.1111/anae.15093.
9. Thompson KA, Pappachan JV, Bennett AM, et al. Influenza aerosols in UK hospitals during the H1N1 (2009) pandemic—the risk of aerosol generation during medical procedures. PLoS One. 2013. PMID: 23418548.

10. Tellier R, Li Y, Cowling BJ, Tang JW. Recognition of aerosol transmission of infectious agents: a commentary. BMC Infect Dis. 2019;19, 101-101.
11. Mizumoto K, Kagaya K, Zarebski A, et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020. PMID: 32183930.
12. Nishiura H, Kobayashi T, Miyamaet T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020. PMID: 32179137 f.
13. Inui S, Fujikawa A, Jitsu M, Kunishima N, et al. Chest CT findings in cases from the cruise ship ''Diamond Princess'' with Coronavirus Disease 2019 (COVID-19). Radiol: Cardiothorac Imaging. 2020;2(2):e200110.
14. Zou L, Ruan F, Huanget M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020. PMID: 32074444.
15. Seijo LM, Sterman DH. Interventional pulmonology. NEJM. 2001;344(10):740–9.
16. WHO Technical guidance. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/infection-prevention-and-control, 2020 (accessed on 15th June 2020).
17. Centers for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings. CDC. 13 April 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html (accessed on 15th June 2020).
18. Baldwin D.R., Lim W.S., Rintoul R., Navani N., Fuller L., Woolhouse I., et al. Recommendations for day case bronchoscopy services during the COVID-19 pandemic. British Thoracic Society. Version 1.2. March 2020.
19. World Health Organization. Health Systems Respond to COVID-19 Technical Guidance #2 Creating surge capacity for acute and intensive care Recommendations for the WHO European Region 6 April 2020.
20. Adhikari U, Chabrelie A, Weir M, Boehnke K, McKenzie E, Ikner L, et al. A case study evaluating the risk of infection from middle eastern respiratory syndrome coronavirus (MERS-CoV) in a hospital setting through Bioaerosols. Risk Anal. 2019;39(12):2608–24.
21. American Institute of Architects. Guidelines for design and construction of hospital and health care facilities, 2001. Washington, DC: American Institute of Architects Press; 2001.
22. Rutala WA, Weber DJ. Disinfection of endoscopes: review of new chemical sterilants used for high-level disinfection. Infect Control Hosp Epidemiol. 1999;20:69–76.
23. Wahidi MM, Lamb C, Murgu S, et al. American Association for Bronchology and Interventional Pulmonology (AABIP) statement on the use of bronchoscopy and respiratory specimen collection in patients with suspected or confirmed COVID-19 infection. March 9, 2020 and expert consensus of the AABIP COVID-19 Task Force. J Bronchology Interv Pulmonol. 2020;(March), http://dx.doi.org/10.1097/LBR.0000000000000681 https://aabronchology.org/wp-content/uploads/2020/03/2020-AABIP-Statement-on-Bronchoscopy-COVID.GAE-updated-Version.pdf (accessed on 15th june 2020.
24. Centers for Disease Control and Prevention. Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008. May 2019 update. https://www.cdc.gov/infectioncontrol/pdf/guidelines/disinfection-guidelines-H.pdf (accessed on 15th june 2020).
25. Chen CC, Chi CY. Biosafety in the preparation and processing of citology specimens with potential coronavirus (COVID-19) infection: perspective from Taiwan. Cancer Cytopathol. 2020;128(May (5)):309–16.
26. Tran K, Cimon K, Severn M, et al. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One. 2012;7:e35797.
27. Healthcare Infection Control Practices Advisory Committee. Essential Elements of a Reprocessing Program for Flexible Endoscopes – The Recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC). 2016. https://www.cdc.gov/hicpac/pdf/flexible-endoscopereprocessing.pdf (accessed on 15th June 2020).
28. Pritchett MA, Oberg CL, Belanger A. Society for advanced bronchoscopy consensus statement and guidelines for bronchoscopy and airway management amid the COVID-19 pandemic. J Thorac Dis. 2020;12(5):1781–98.
29. World Health Organization (WHO). Laboratory testing for Coronavirus Disease 2019 (COVID-19) in suspected human cases: interim Guidance, 19March 2020. https://www.who.int/publications/i/item/10665-331501 (accessed on 15th June 2020).
30. Mazzone PJ, Gould MK, Arenberg DA, et al. Management of lung nodules and lung cancer screening during the COVID-19 pandemic: CHEST Expert Panel Report. Chest. 2020;(April), http://dx.doi.org/10.1016/j.chest.2020.04.020, pii: S0012-3692(20)30758-3.
31. Wahidi M.M., Lamb C., Murgu S., et al. March 19th, 2020 Update to the American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection. https://aabronchology.org/wp-content/uploads/2020/03/AABIP-Statement-on-Bronchoscopy-COVID_3-12-2020-Statement-plus-3-19-2020-updates-V3.pdf (accessed on 15th June 2020).
32. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239–42.
33. Ding Q, Lu P, Fan Y, et al. The clinical characteristics of pneumonia patients co-infected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020;(March), http://dx.doi.org/10.1002/jmv.25781.
34. Hellyer TP, McAuley DF, Walsh TS, et al. Biomarker-guided antibiotic stewardship in suspected ventilator-associated pneumonia (VAPrapid2): a randomised controlled trial and process evaluation. Lancet Respir Med. 2020;8(2):182–91.
35. Biselli P, Fricke K, Grote L, et al. Reductions in dead space ventilation with nasal high flow depend on physiological dead space volume: metabolic hood measurements during sleep in patients with COPD and controls. Eur Respir J. 2018;51(5): 1702251.
36. Batra H, Yannus L. Indications and complications of rigid bronchoscopy. Expert Rev Respir Med. 2018;12(June (6)):509–20.
37. Pathak V, Welsby V, Mahmood K, et al. Ventilation and anesthetic approaches for rigid bronchoscopy. Ann Am Thorac Soc. 2014;11(May (4)):628–34.
38. Pitiot V, Grall M, Ploin D, et al. The use of CT-scan in foreign body aspiration in children: a 6 years' experience. Int. J. Pediatr. Otorhinolaryngol. 2017;102:169–73.
39. Ahmed OG, Guillerman RP, Giannoni CM. Protocol incorporating airway CT decreases negative bronchoscopy rates for suspected foreign bodies in pediatric patients. Int J Pediatr Otorhinolaryngol. 2018;109:133–7.
40. Yarmus L, Feller-Kopman D. New bronchoscopic instrumentation: a review and update in rigid bronchoscopy. In: Beamis JF, Mathur PN, Mehta AC, editors. Interventional pulmonary medicine. Lung biology in health and disease 230. New York: Informa Healthcare; 2010. p. 1–9.
41. Zhu J, Zhong Z, Li H, et al. CT imaging features of 4,121 patients with COVID-19: a meta-analysis. J Med Virol. 2020, http://dx.doi.org/10.1002/jmv.25910 [Epub ahead of print].

42. Salehi S, Abedi A, Balakrishnan S, et al. Coronavirus disease 2019 (covid-19): a systematic review of imaging findings in 919 patients. AJR Am J Roentgenol. 2020;(March):1–7.
43. Lin C, Ding Y, Xie B, Sun Z, Li X, Chen Z, et al. Asymptomatic novel coronavirus pneumonia patient outside Wuhan: the value of CT images in the course of the disease. Clin Imaging. 2020;63:7–9.
44. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;(January). S0140-6736(20)30211-30217.
45. Sun R, Liu H, Wang X. Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of covid-19 pneumonia. Korean J Radiol. 2020;(March), http://dx.doi.org/10.3348/kjr.2020.0180 [Epub ahead of print].
46. Aiolfi A, Biraghi T, Montisci A, et al. Management of persistent pneumothorax with thoracoscopy and blebs resection in covid-19 patients. Ann Thorac Surg. 2020;(April). S0003-4975(20)30604-4.
47. Peng Q, Wang X, Zhang L. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic. Intensive Care Med. 2020;46(May (5)):849–50.
48. Recomendações da Sociedade Portuguesa de Pneumologia e do Grupo de Estudos de Cancro do Pulmão na abordagem dos doentes com Cancro do Pulmão durante a Pandemia de COVID-19. https://www.sppneumologia.pt/uploads/subcanais_conteudos_ficheiros/orientacoes-da-ct-de-pneumologia-oncologica-da-spp-no-cancro-do-pulmao-durante-a-pandemia-de-covid-19.pdf (accessed on 15th June 2020).
49. Hallifax R., Wrightson J.M., Bibby A., et al. Pleural services during the COVID-19 Pandemic. British Thoracic Society. https://www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community (accessed on 15th June 2020).
50. Centers for Disease Control and Prevention. Healthcare Infection Prevention and Control FAQs for COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-faq.html (accessed on 15th June 2020).
51. Society of Interventional Radiology. Aerosol Generating Procedures Performed by Interventional Radiology Clinical Notification from the Society of Interventional Radiology. https://www.sirweb.org/practice-resources/covid-19-resources/covid-19-clinical-notification-3-26-20 (accessed on 15th June 2020).

Pulmonol. 2020;**26(6)**:398–417

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Endobronchial ultrasound-transvascular needle aspiration (EBUS-TVNA) in the diagnosis of a hilar metastasis of an extrapulmonary neoplasm

To the Editor,

Convex-probe endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) and esophageal ultrasound with ultrasound bronchoscope (EUS-B) are nowadays the interventional pulmonology cornerstone of non-small-cell lung cancer mediastinal and hilar staging; these techniques also allow the diagnosis of mediastinal and hilar involvement related to extrapulmonary primary neoplasms, infections and inflammatory diseases.

Mediastinal and hilar lymph node stations beyond major mediastinal blood vessels, without direct contact with the tracheobronchial tree, are not routinely accessed through EBUS-TBNA or EUS-B, especially due to procedural safety concerns.[1] However, since 2007, there have been several case reports and series presenting endoscopic transvascular needle aspiration (TVNA) as a feasible and safe technique.[2–4]

To the best of our knowledge, we are reporting the first Portuguese case of a technically successful hilar lymph node sampling through EBUS-TVNA, resulting in a definitive cytological diagnosis.

A 76-year-old man, former smoker (45 pack-years), retired from metallurgical industry, with a previous medical history of arterial hypertension, atrial fibrillation under anticoagulant therapy and dyslipidemia, experienced onset of neck pain, hoarseness and progressive exertional dyspnea. The patient presented an Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade equal to 1. Constitutional symptoms, anorexia or dysphagia were absent. Neck and chest CT scan revealed a 2 cm-sized nodular lesion in the right lateral wall of the hypopharynx and unsuspicious mediastinal and hilar lymph nodes. A pharyngeal biopsy was diagnostic for invasive squamous cell carcinoma of the hypopharynx (T2N2aM0, stage IV-A). Chemotherapy and radiation therapy led to favorable clinical and imaging responses.

Fourteen months after the initial diagnosis, a follow-up chest CT scan identified 'de novo' small left pleural effusion and a 2 cm-sized left hilar lymph node suspicious for metastasis (Fig. 1). There was a multidisciplinary consensus decision to perform diagnostic bronchoscopy and EBUS-TBNA.

In our center, we perform EBUS under general anesthesia. Anticoagulant therapy has been properly preemptively discontinued. Fiberoptic bronchoscopy performed before EBUS was normal. A systematic inspection of mediastinal and hilar lymph node stations was performed through EBUS according to the European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS).[5] The left interlobar (11 L) lymph node station was the only one warranting sampling due to suspicious imaging criteria; however, color Doppler ultrasound showed the need for TVNA to reach the lymph node station (Fig. 2). We used a 22-gauge EBUS needle to perform a transvascular puncture of the 11 L lymph node station. A good quality sample was obtained after one pass; thus, no further needle passes were done. Rapid on-site cytological evaluation (ROSE) was not performed due to the unavailability of this technique in our institution. No post-procedural complications occurred, allowing the patient to be discharged home after a short period of clinical surveillance.

Cytological analysis of the sampled lymph node station was diagnostic for mediastinal metastasis of squamous cell carcinoma. No immunohistochemical or mutational analysis was performed because at the time, in our institution, these techniques were available only for histological specimens. Second-line therapy with immunotherapy was started and the patient remains under treatment and follow-up.

Currently, EBUS-TVNA is not included in mediastinal or hilar assessment as it should not be performed routinely until prospective data becomes available. Additionally, it should be only executed by experienced bronchoscopists in carefully selected patients and procedural settings.

Declarations of interest

None

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

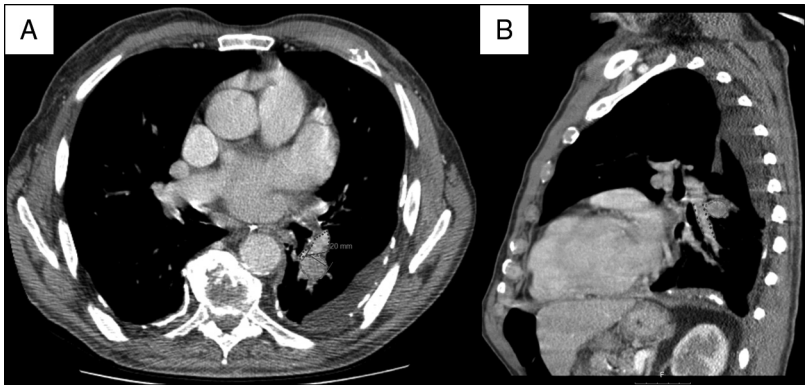


Fig. 1 Contrast-enhanced chest CT scan images (A: axial image; B:sagittal image) showing the anatomical relationships between the interlobar branch of the left pulmonary artery (outlined by blue dots), the 11 L lymph node station (outlined by red dashed lines) and the left lower lobe bronchus. Note that, in this patient, the 11 L lymph node station does not have direct contact with the bronchial wall.

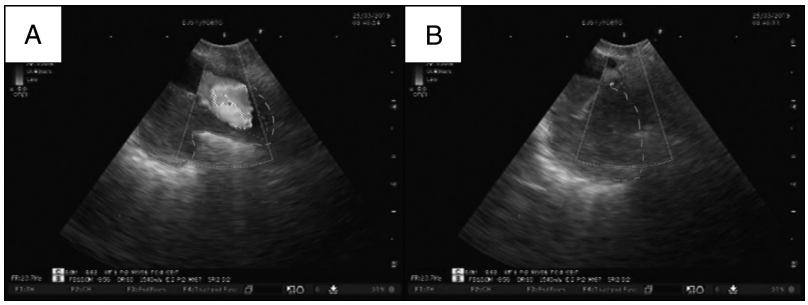


Fig. 2 EBUS-TBNA color Doppler ultrasound images of the transvascular puncture of the 11 L lymph node station: the left pulmonary artery branch is outlined by blue dots and the 11 L lymph node station is roughly outlined by red dashed lines. A: the lymph node does not have any direct contact with the bronchial wall due to the interposition of the left pulmonary artery branch. B: the EBUS needle traversed the vessel and successfully reached the lymph node.

References

1. Kazakov J, et al. Endobronchial and endoscopic ultrasound-guided transvascular biopsy of mediastinal, hilar, and lung lesions. Ann Thorac Surg. 2017;103(3):951–5.
2. Wallace MB, et al. Transaortic fine-needle aspiration of centrally located lung cancer under endoscopic ultrasound guidance: the final frontier. Ann Thorac Surg. 2007;84(3):1019–21.
3. Mehta RM, et al. Defining expanded areas in EBUS sampling: EBUS guided trans- and intra-pulmonary artery needle aspiration, with review of transvascular EBUS. Clin Respir J. 2018;12(5):1958–63.
4. Panchabhai TS, et al. Endobronchial Ultrasound-guided Transvascular Needle Aspiration: A Single-Center Experience. J Bronchology Interv Pulmonol. 2015;22(4):306–11.
5. Vilmann P, 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). Endoscopy. 2015;47(06):545–59.

Fernando Guedes[a,b,c,*], Tiago Oliveira[a,b]

[a] *Pulmonology Department, Centro Hospitalar Universitário do Porto – Hospital de Santo António, Largo do Prof. Abel Salazar, 4099-001 Porto, Portugal*
[b] *Abel Salazar Institute of Biomedical Sciences, University of Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal*
[c] *Centro de Estudos de Ciência Animal (CECA), Instituto de Ciências, Tecnologias e Agroambiente (ICETA) da Universidade do Porto, Praça Gomes Teixeira, Apartado 55142, 4051-401, Porto, Portugal*

[*] Corresponding author.
E-mail address: fernando.t.guedes@gmail.com (F. Guedes).

1 November 2019
Available online 24 December 2019

https://doi.org/10.1016/j.pulmoe.2019.11.005

Cystic tuberculosis: a very unusual aspect of a common disease

Introduction

Increase in cases of tuberculosis have been reported in recent years in several countries, particularly in urban centers and regions with high prevalence of HIV infection.[1] With this worldwide resurgence of *M. tuberculosis* infection, the recognition of complications and sequelae is very important. Patients with pulmonary tuberculosis present a wide range of CT findings, including airspace or interstitial nodules, the tree-in-bud pattern, consolidations, cavitation, fibrosis, bronchial wall thickening, lymph node enlargement, and pleural effusion.[2] However, cystic changes associated with pulmonary tuberculosis have rarely been reported, and are among the rarest presentations of this common disease.[3–8]

The aim of this report was to describe a case of cystic tuberculosis and to perform a review of the previous reports of this uncommon finding. The MEDLINE database was searched for articles that were published between January 1994 and October 2019. All searches were performed using medical subject heading (MeSH) or free text word. We combined search terms for the primary disease (tuberculosis), the diagnostic test (computed tomography) and pattern (cystic disease). We also manually searched the reference lists of the eligible studies.

Case report

A 28-year-old homeless woman, a drug-user was admitted to the Emergency Department in an inebriated state under the influence of alcohol. On physical examination, she was found to be disoriented and to have a persistent cough. Her laboratory test results were unremarkable. Chest computed tomography (CT) showed bizarre, irregular cystic formations in the upper regions of the lungs associated with ill-defined centrilobular nodules (Fig. 1). Based on this tomographic pattern, the initial diagnostic suspicion was Langerhans cell histiocytosis.

After clinical improvement, when the patient was lucid and oriented, she reported that she had been admitted to a hospital in a nearby city and diagnosed with pulmonary tuberculosis 9 months previously. We contacted the hospital and obtained the following information: the patient presented with complaints of fever for 2 months, productive cough, shortness of breath, asthenia, and 12 kg weight loss. The patient's sputum was positive for acid-fast bacilli, and a culture was positive for *Mycobacterium tuberculosis*. A human immunodeficiency virus (HIV) test also yielded positive findings. The patient was treated with antituberculous drugs for 6 months. A CT examination performed at that time (9 months before the current examination) showed diffuse multiple small nodules, some of which were cavitated, in the upper lobes (Fig. 2). Thus, the final diagnosis was pulmonary tuberculosis evolving into cystic formations.

Discussion

Our patient initially presented with disseminated tuberculosis, which evolved to cystic lesions, predominantly in the upper lung zones. Cystic lesions may develop before or during antituberculous treatment in patients with pulmonary tuberculosis.[5] Tuberculosis cysts may evolve with varied outcomes and severity during the course of the disease.[4] In some cases, the cysts are reversible and disappear almost completely after antituberculous therapy; in others, the cysts persist after treatment.[3,4,6] The rupture of these cystic lesions may cause pneumothorax[7] or pneumomediastinum.[6]

Several mechanisms have been suggested for the pathogenesis of cystic lung lesions due to tuberculosis: a) a check-valve mechanism due to the granulomatous involvement of bronchioles and the excavation of caseous necrotic material by bronchial drainage;[3,4–7] b) the communication of tuberculous lesions containing caseous necrosis with the bronchi, resulting in the excavation of necrotic material and cystic changes;[7] and c) the cystic lesions representation of areas of dilated bronchioles. Immunohistochemical studies and electron microscopic examinations have revealed that the proteinases secreted from the inflammatory cells of peribronchiolar granulomas are partly responsible for the degradation of elastic fibers along the bronchioles, alveolar ducts, and alveolar walls.[5,7]

On CT, these cysts appear predominantly in the upper and middle lung zones. The cystic lesions are associated with centrilobular nodules and branching opacities in surrounding areas.[2,7] The lesions are irregular in shape, increase in size, and have a tendency to coalesce. The upper zone predominance may be related to the fact that tuberculous lesions are more common in this region.[6]

Pulmonary tuberculosis with multiple cysts should be differentiated from various cystic lung diseases, particularly Langerhans cell histiocytosis, lymphangioleiomyomatosis, lymphocytic interstitial pneumonia, and *Pneumocystis jiroveci* pneumonia,[2,6] and from diseases that mimic cysts, such as bullous emphysema and pneumatoceles.[4] In the proper clinical context, cystic changes in pulmonary tuberculosis can be easily diagnosed.[3] In our patient, the main differential diagnosis was Langerhans cell histiocytosis, particularly because of the upper lobe predominance of the cysts. In summary, pulmonary tuberculosis may on rare occasions present as cystic lung disease and should be recognized as a possible cause of acquired cystic lung disease in appropriate clinical settings (Table 1).

Authors' contributions

JP, ESP, EM were responsible for the conception and design of the study, and wrote and edited the manuscript. EM contributed to the drafting and revision of the manuscript. All authors read and approved the final manuscript.

Table 1 Cases of cystic tuberculosis previously described in the literature.

Author and year of publication	Study design	Main findings
Ko et al.[6]	Case Reports	Case 1. Female, 26 y.o, HIV (-) Fever, cough, dyspnea Sputum, BAL and culture (+) CT: micronodules; consolidations; ground-glass; cavitation Control CT (8 months): nearly complete disappearance of cystic lesions; areas of irregular lines. Case 2. Female, 27 y.o, HIV (-) Fever, cough, dyspnea, loss of weight Sputum and biopsy (+) CT: cysts in upper lobes; consolidations Control CT (8 months): nearly complete disappearance of cystic lesions; irregular lines and centrilobular lesions in the right lung. Case 3. Female, 52 y.o, HIV (-) Fever, cough, dyspnea Sputum, BAL and culture (+) CT: micronodules; diffuse ground glass Control CT (6 months): nearly complete disappearance of cysts. remaining micronodules and irregular lines.
Takemura et al.[7]	Case Report	Female, 30 y.o, immunocompromised - HIV (-) Fever, cough, loss of weight - Pneumothorax BAL and culture (+) CT: small cysts in upper lobes Patient died after 5 months
Lee et al.[5]	Case Report	Male, 24 y.o, HIV (-) Fever, cough, dyspnea - Pneumothorax Sputum and culture (+) CT: centrilobular nodules; tree-in-bud pattern; consolidations, Cavitation on the left lung CT control (4 months): cysts larger than previous TC.
Cai et al.[2]	Case Report	Male, 64 y.o, HIV (-) Fever and cough Sputum (-) - BAL and biopsy (+) CT: cysts and bilateral ground glass
Ko et al.[3]	Case Report	Male, 48 y.o, HIV (-) Fever, cough, dyspnea Sputum, BAL and culture (+) CT: micronodules; diffuse ground glass CT control (6 months): reduction of the cystic lesions; fibrosis in the upper lobes
Ray et al.[4]	Case Report	Female, 13 y.o, HIV (-) Fever, dyspnea, loss of weight BAL and culture (+) CT: centrilobular nodules; multiple cysts and diffuse ground glass. CT control (6 months): reduction of the cysts, nodules and opacities.
Periwal et al.[8]	Case Report	Female, 14 y.o, HIV (-) Fever, loss of weight - pneumothorax BAL and culture (+) CT: cysts and bilateral ground-glass.

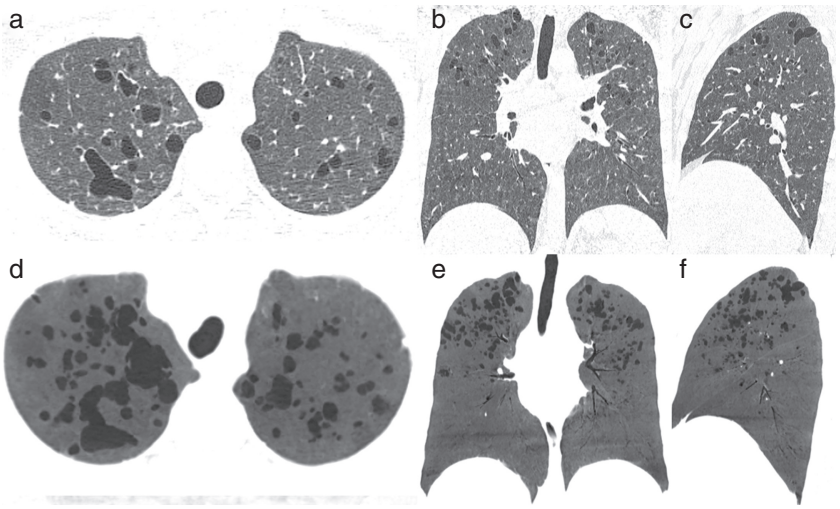


Fig. 1 Axial (A), coronal (B), and sagittal (C) reformatted CT images showing multiple thin-walled cysts and ill-defined centrilobular nodules, mainly in the upper lung zones. The cysts have bizarre shapes and a branching appearance. (D–F) Minimum intensity projection reformatted images in the same planes as A–C better demonstrate the thin-walled bizarre cysts.

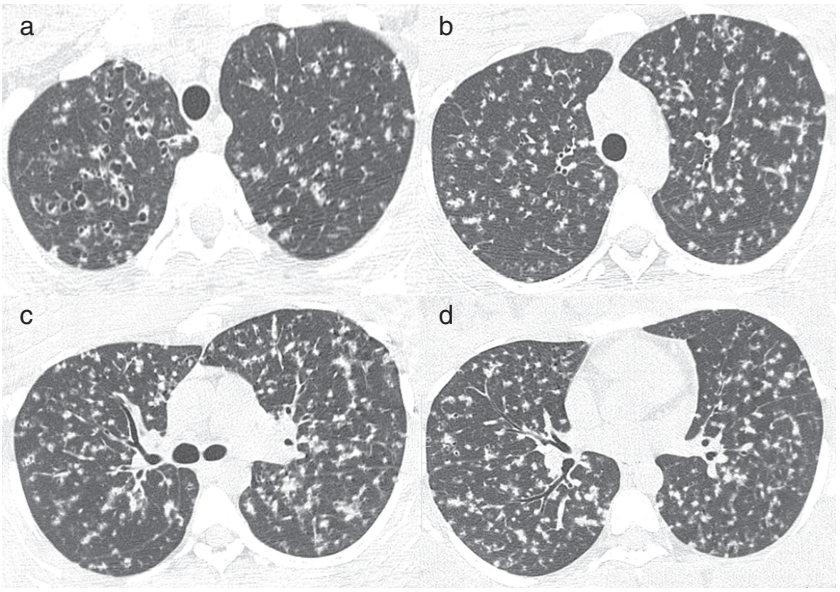


Fig. 2 Axial CT images obtained 9 months before those presented in Fig.1 show diffuse multiple small nodules, some of which are cavitated, in the upper lobes.

Conflicts of interest

The author has no conflicts of interest to declare.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding

This study was undertaken without funding.

References

[1] Belknap RW. Current medical management of pulmonary tuberculosis. Thorac Surg Clin. 2019;29:27–35.

[2] Cai HR, Cao M, Meng FQ, Li WC. Cystic changes associated with pulmonary tuberculosis: a case report. Chin Med J (Engl). 2006;119:1125–8.

[3] Ko SM, Seo SJ, Choi WI, Jeon YJ. Cystic change in pulmonary tuberculosis in an immunocompetent adult: a case report. J Korean Radiol Soc. 2008;58:261–4.

[4] Ray A, Suri JC, Sen MK, Khanna A. Cystic lung disease in tuberculosis: an unusual presentation. Lung India. 2013;30:351–3.

[5] Lee HJ, Goo JM, Im JG. Rapid and irreversible cystic change of pulmonary tuberculosis in an immunocompetent adult. J Thorac Imaging. 2003;18:254–6.

[6] Ko KS, Lee KS, Kim Y, Kim SJ, Kwon OJ, Kim JS. Reversible cystic disease associated with pulmonary tuberculosis: radiologic findings. Radiology. 1997;204:165–9.

[7] Takemura T, Akiyama O, Yanagawa T, Ikushima S, Ando T, Oritsu M. Pulmonary tuberculosis with unusual cystic change in an immunocompromised host. Pathol Int. 2000;50:672–7.

[8] Periwal P, Khanna A, Gothi R, Talwar D. Bronchocentric granulomatosis with extensive cystic lung disease in tuberculosis: An unusual presentation. Lung India. 2016;33:320–2.

Joane Perim, Eduardo Scarlatelli Pimenta, Edson Marchiori*

Department of Radiology – Federal, University of Rio de Janeiro, Rua Thomaz Cameron, 438. Valparaiso. CEP 25685.120, Petrópolis. Rio de Janeiro, Brazil

* Corresponding author.
E-mail address: edmarchiori@gmail.com (E. Marchiori).

1 December 2019

https://doi.org/10.1016/j.pulmoe.2019.12.001

Diffuse cystic lung disease as the primary tomographic manifestation of bronchiolitis: A case series

To the Editor,

The differential diagnosis of diffuse cystic lung diseases (DCLDs) includes a wide range of etiologies with different underlying pathophysiologic mechanisms.[1,2] Although morphological features, such as shape, distribution within the lung parenchyma and adjacent structures, and the presence of other pulmonary manifestations may suggest a specific underlying disease, a significant overlap exists between tomographic findings from different etiologies. In these cases, a lung biopsy may be required to establish a diagnosis.[1,2]

Lymphangioleiomyomatosis (LAM) is a rare slowly progressive neoplastic lung disease, which has a characteristic radiological appearance and affects mainly women of childbearing age. However, in women with regular and thin-walled cysts without extrapulmonary features compatible with LAM and with low levels of serum vascular endothelial growth factor D (VEGF-D), other potential rare etiologies may be included in the differential diagnosis, such as bronchiolitis, and smoking-related DCLDs.[3–5] We present the cases of eight women that were initially suspected with LAM whose histopathological analysis was compatible with bronchiolitis.

Among 347 patients with DCLDs followed at our center since 2006, eight (2.3%) had diffuse pulmonary cysts on HRCT and a histological diagnosis of cellular and constrictive bronchiolitis and were assessed in this study. Clinical, functional, tomographic, and histological features were analyzed. Written informed consent was obtained from all patients.

Pulmonary function tests adhered to recommended guidelines.[6–8] Computed tomography was performed in a supine position. Quantification of the volume of the cystic lesions was obtained automatically by densitovolumetry using a computer program (Advantage Workstation Thoracic VCAR software; GE Medical Systems, Milwaukee, WS, USA) and by selecting pixels between −1000 and −950 HU on soft tissue filter images. Paraffin blocks of lung tissue were retrieved for histological analysis (hematoxylin and eosin stain). Immunohistochemical staining for smooth muscle actin (SMA) and human melanoma black-45 (HMB-45) antibodies were examined.

Clinical and functional features at the time of lung biopsy are summarized in Table 1. All patients were non-smoking

Table 1 Demographic, clinical and functional characteristics (n = 8).

Female	8 (100%)
Age at diagnosis (years)	43 ± 14
Time between onset of symptoms and diagnosis (years)	2 ± 2
Current or former smokers	0
Environmental exposure	4 (50%)
Previous (mold and birds)	2 (25%)
Current (only birds)	2 (25%)
Clinical manifestations at diagnosis	
Dyspnea	6 (75%)
mMRC	1 (0–1)
Cough	4 (50%)
Wheezing	1 (12.5%)
Pneumothorax	1 (12.5%)
Pleuritic chest pain	2 (25%)
Xerostomy	2 (25%)
Xerophtalmia	1 (12.5%)
Skin lesions	0
SpO_2 on room air (%)	97 ± 2
Oxygen use	0
Pulmonary function tests	
FVC (L)	3.01 ± 0.73
FVC (%predicted)	88 ± 12
FEV_1 (L)	2.32 ± 0.85
FEV_1 (%predicted)	79 ± 23
FEV_1/FVC	0.73 ± 0.14
DLCO (mL/min/mmHg)	18.2 ± 4.6
DLCO (%predicted)	76 ± 17
Functional patterns	
Normal spirometry	5 (63%)
Obstructive	2 (25%)
Restrictive	1 (12%)
Air trapping[a]	2 (29%)
Reduced DLCO	3 (38%)
Positive response to BD[b]	1 (17%)

Values are expressed as mean ± SD, median (25th–75th percentiles) or n (%).
Definition of abbreviations: BD: bronchodilator; DLCO: carbon monoxide diffusing capacity; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; mMRC: modified medical research council dyspnea scale; SpO_2: oxyhaemoglobin saturation by pulse oximetry.
[a] Information available for 7 patients.
[b] Information available for 6 patients.

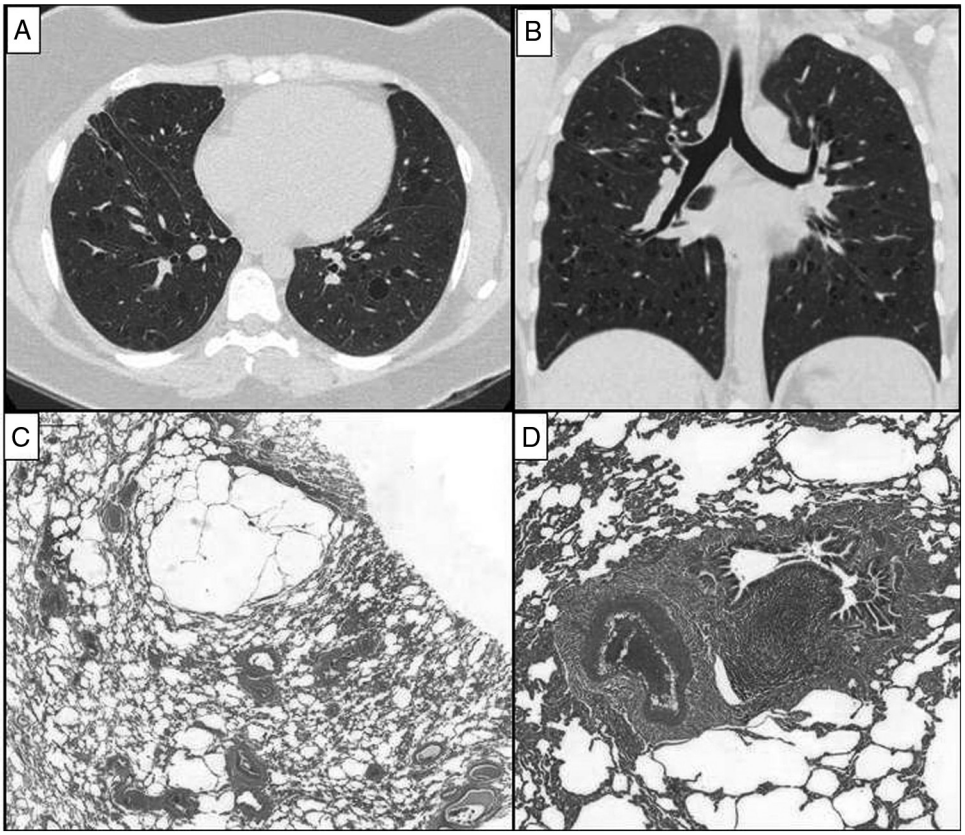


Figure 1 Chest HRCT scans (A and B) and histopathological findings (C and D) of a 38-year-old woman with chronic cellular bronchiolitis and diffuse cystic lung disease. (A) Axial CT image shows diffuse, regular, and thin-walled pulmonary cysts. The quantification of cystic lung lesions is depicted in blue (B). The percentage of the total lung area occupied with cysts is 2.75%. The photomicrographies (C and D) show mild inflammatory mononuclear cells infiltrating some of the bronchiolar walls. There are cystic alveolar changes in the nearby parenchyma tissue. Lymphoid follicles with reactive germinal centers are shown (hematoxylin and eosin stain) (D). Magnifications: C. $\times$13; D. $\times$70.

women with a mean age of 43 ± 14 years at diagnosis. The most common symptom was dyspnea (75%). Four patients had a relevant exposure history. No patient had any relevant personal or family medical history. Anti-Sjögren syndrome-related antigen A/Ro or B/La antibodies, the rheumatoid factor, and antinuclear antibodies were negative. Serum inflammatory markers, and immunoglobulins were unremarkable.

Mean FEV_1 and DLCO were $79 \pm 23\%$ predicted, and $76 \pm 17\%$ predicted, respectively. An obstructive pattern and reduced DLCO were found in 25% and 38% of patients, respectively.

All patients showed diffusely distributed multiple, regular thin-walled cysts on HRCT (Fig. 1). Other tomographic patterns were not found. Four patients underwent HRCT to investigate respiratory symptoms while in the remaining, pulmonary cysts were incidentally found during an investigation of abdominal pain or a routine exam of the chest. The median tomographic extent of cysts was 2.51% (interquartile 25%–75%: 0.8%–8.9%). Serum VEGF-D levels were available for only two patients (139 and 407 pg/mL).

All patients underwent a surgical lung biopsy. Histological analysis showed evidence of chronic cellular (Fig. 1) or constrictive bronchiolitis. Six cases had inflammatory mononuclear cells infiltrating the bronchiolar wall with a patchy distribution and variable intensity. Biopsies of two patients displayed infrequent, poorly formed and randomly distributed non-necrotizing granulomas. Two patients presented bronchiolar fibrosis. One patient had a discreet fibrotic thickening of the submucosa associated with luminal narrowing in some small airways, whereas another patient displayed complete focal obliteration of the bronchiolar lumen with fibrous scar formation. All patients presented with parenchymal cysts characterized by airspace distensions in the centrilobular and subpleural regions. The walls of these lesions contained residual alveolar tissue. Proliferation of immature smooth muscle-like cells was not detected.

DCLDs have a broad differential diagnosis. Clinical and tomographic findings combined with a multidisciplinary approach make differentiation of various entities possibile. In our study, we described eight women with DCLDs referred with an initial suspicion of LAM. Following a histopathological analysis they were diagnosed as having cellular or constrictive bronchiolitis, with mild severity, which is a very rare etiology for DCLD. Although suggestive, the tomo-

graphic patterns of the diffuse, regular and thin-walled cysts in women are not specific to LAM.[2,4,5] In the absence of definite findings, a pulmonary biopsy is mandatory to diagnose LAM.[3] Low availability of serum VEGF-D dosage is a limitation of our study.

Some findings on HRCT contribute to establishing the etiology of DCLDs. In pulmonary Langerhans histiocytosis, cysts are usually irregular, predominate in the upper and middle lung zones and may be associated with nodules.[1,2] In Birt-Hogg-Dubé (BHD) syndrome, cysts are multiple, thin-walled and predominantly basilar and paramediastinal.[1,2] Cysts in lymphocytic interstitial pneumonia occur in the lower lobes along the peribronchovascular bundle, frequently with ground-glass opacities.[2]

The typical pathological and immunohistochemical features of LAM were not identified in our study. Histologically, LAM nodules consist of two cellular subpopulations: the spindle cells express SMA and forms the core of the nodules surrounded by epithelioid cells that exhibit immunoreactivity for HMB-45 antibody.[9] On histopathology, the morphology of BHD cysts may resemble what was found in our cases. However, we excluded BHD based on clinical and tomographic features.[10] Cysts, emphysema, and respiratory bronchiolitis are identified in smoking-related DCLDs, but were not found in our study.[5] A combination of the DCLDs and small airway disease is mainly identified in specific conditions, such as Sjögren's syndrome, and it is thought that chronic small airway damage might lead to cyst formation in these patients. A possible explanation for the lung cyst formation in bronchiolitis is a check-valve obstruction with distal airspace overinflation related to air trapping, distal to the abnormal airways.[1,2]

In two cases, histological analysis showed evidence of chronic cellular bronchiolitis associated with infrequent, poorly formed, non-necrotizing granulomas, frequently seen in hypersensitivity pneumonitis (HP). Pulmonary cysts have been described in HP possibly due to partial bronchiolar obstruction.[2]

Potential etiologies for our patients with bronchiolitis include autoimmune disorders, such as Sjögren syndrome, post viral infections and HP. However, none of the etiologies raised were confirmed.

In summary, LAM is a prototypical DCLD with a characteristic appearance on HRCT. However, cystic features alone are inadequate to establish a diagnosis of LAM. In such context, bronchiolitis should be considered in the differential diagnosis of DCLDs.

Informed consent

Patients gave informed consent for this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. Diffuse cystic lung disease. Part II. Am J Respir Crit Care Med. 2015;192(1):17–29, http://dx.doi.org/10.1164/rccm.201411-2096CI.
2. Baldi BG, Carvalho CRR, Dias OM, Marchiori E, Hochhegger B. Diffuse cystic lung diseases: differential diagnosis. J Bras Pneumol. 2017;43(2):140–9, http://dx.doi.org/10.1590/S1806-37562016000000341.
3. Gupta N, Finlay GA, Kotloff RM, Strange C, Wilson KC, Young LR, et al. Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2017;196(10):1337–48, http://dx.doi.org/10.1164/rccm.201709-1965ST.
4. Rowan C, Hansell DM, Renzoni E, Maher TM, Wells AU, Polkey MI, et al. Diffuse cystic lung disease of unexplained cause with coexistent small airway disease: a possible causal relationship? Am J Surg Pathol. 2012;36(2):228–34, http://dx.doi.org/10.1097/PAS.0b013e318237c599.
5. Gupta N, Colby TV, Meyer CA, McCormack FX, Wikenheiser-Brokamp KA. Smoking-related diffuse cystic lung disease. Chest. 2018;154(2):e31–5, http://dx.doi.org/10.1016/j.chest.2018.02.027.
6. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720–35, http://dx.doi.org/10.1183/09031936.05.00034905.
7. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38, http://dx.doi.org/10.1183/09031936.05.00034805.
8. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511–22, http://dx.doi.org/10.1183/09031936.05.00035005.
9. Zhang X, Travis WD. Pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med. 2010;134(12):1823–8, http://dx.doi.org/10.1043/2009-0576-RS.1.
10. Koga S, Furuya M, Takahashi Y, Tanaka R, Yamaguchi A, Yasukufu K, et al. Lung cysts in Birt-Hogg-Dubé syndrome: histopathological characteristics and aberrance sequence repeats. Pathol Int. 2009;59(10):720–8, http://dx.doi.org/10.1111/j.1440-1827.2009.02434.x.

M.R. de Oliveira, O.M. Dias, A.F. Amaral

Divisao de Pneumologia, Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

E.C.T. do Nascimento

Departamento de Patologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

M. Wanderley

Departamento de Radiologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

C.R.R. Carvalho, B.G. Baldi*

Divisao de Pneumologia, Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

*Corresponding author at: Dr Eneas de Carvalho Aguiar Avenue, 44, Fifth Floor, Sao Paulo 05403-900, Brazil.

E-mail address: bruno.guedes2@terra.com.br (B.G. Baldi).

24 November 2019

https://doi.org/10.1016/j.pulmoe.2020.01.006

A rare case of pulmonary disease combining alpha-1-antitrypsin deficiency and common variable immunodeficiency

Dear Editor,

Alpha-1-antitrypsin (AAT) is a glycoprotein synthetized mainly by the liver, acting primarily in the lung as an inhibitor of neutrophil elastase, but also capable of regulating other proteases.[1,2]

Alpha-1-antitrypsin deficiency (AATD) is a genetic disorder inherited in an autosomal codominant pattern, which is estimated to affect in Europe 1 in 2700 (Northern Europe) to 18,000 (Central Europe).[3–5] AATD increases the risk of chronic obstructive pulmonary disease (COPD), emphysema and chronic bronchitis, liver cirrhosis, panniculitis and c-ANCA (anti-neutrophil cytoplasmic antibodies) positive vasculitis, due to a proteolytic imbalance and/or negative effect of protein polymerization.[6]

Pathogenic mutations in *SERPINA1* gene (14q32.13) are the cause of AATD and whereas common M alleles are associated with normal concentrations in the serum, S and Z variants' have decreased circulating levels of AAT (60% and 15% of the normal values, respectively).[1] Most AATD cases are attributed to PI*ZZ genotypes (∼95%) and the remaining ones to PI*SZ, PI*MZ, or any genotype combining rare deleterious mutations.[7] To date, there are more than 130 alleles described in the literature, most of them associated with a significant decrease in AAT circulating levels (deficiency variants) or leading to a total absence of protein (null alleles).[8,9] One of these variants is the PI*Mmalton (p.Phe52del in a M2 allele) that has been found to polymerize and to accumulate in the endoplasmic reticulum, being secreted into the bloodstream in less than 15% of normal AAT concentration.[1] Beside S and Z allele, p.Phe52del (PI*Mmalton or PI*Mpalermo if in a M1alele) appears to be the next most prevalent variant among AATD cases in Iberian Peninsula (54% in Spain and 40% in Portugal).[7–10]

On the other hand, common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by low serum concentration of immunoglobulins which may lead to assorted clinical features,[11] mainly recurrent bacterial infections of respiratory and gastrointestinal tracts.[12] CVID affects approximately 1 in 30,000 individuals and it is the second most common primary immunodeficiency in humans.[12] This disorder is highly heterogeneous and it basically encompasses a group of primary antibody failure syndromes that can be derived from distinct entities all causing some type of hypogammaglobulinemia. To date CVID diagnosis continues to be essentially done by different exclusion criteria.[13] Most cases are sporadic and thought to result from a complex interaction between environmental and genetic factors.[14] Still, in rare instances, CVID m is inherited in an autosomal recessive fashion, and in other rarer cases, the disease can be inherited in an autosomal dominant pattern.[14] Nevertheless, even when CVID is associated with a genetic mutation, additional environmental and genetic risk factors are likely to be necessary for disease onset.[14]

The advent of clinical manifestations and the detection of low levels of immunoglobulins may occur at any age from early childhood to old age.[13] In an European study, 34% of patients presented the disease before the age of 10 years, with male predominance of 2:1 before age 11, and a slight female predominance of 1.3:1 after the age of 30.[13]

So far, only two cases of subjects combining AATD and CVID have been reported.[15,16] Nevertheless, Sansom et al., while studying 43 patients with CVID found five patients with both conditions, suggesting a cumulative effect of AATD and CVID in the presentation of bronchiectasis.[17] In these reports, various A1AT genotypes were evaluated, including various combinations of Z with S and M alleles. Concerning the loss of lung parenchyma few studies have attempted to investigate the impact of sharing these respiratory illnesses. Still a previous work proposed a physical correlation between hypogammaglobulinemia and AATD, later confirmed by another study proving the occurrence of genetic linkage between immunoglobulin heavy constant gamma (Gm markers) loci (*IGHG1-3* genes) and AAT gene (*SERPINA1*).[15]

We present the case of a Portuguese woman, born in Coimbra (Central Portugal) and currently living in Madeira, with history of childhood asthma whose symptoms ceased spontaneously during adolescence. At the age of 32 and having been a tobacco smoker for a decade, the patient was hospitalized for pneumonia with a pleural effusion. Afterwards, respiratory symptoms, such as dyspnea and cough with sputum production become recurrent and multiple respiratory infections were diagnosed within a short time period (five years). In 2000, the patient was found to have CVID upon evaluation of immunoglobulins levels by nephelometry. Consequently, she initiated replacement therapy with subcutaneous immunoglobulin (so currently under 19 years of therapy).

At the age of 57, she was tested for AATD. This analysis showed that she had reduced AAT levels in the blood (18.7 mg/dL by nephelometry) and the initial genetic screening yielded a MM result. Given that the first genetic

Table 1 Patient lung function tests. Prior to AAT augmentation therapy in 2015 and current values. Both results are from post-bronchodilation tests.

Date	FEV1 (L)	FEV1 (%)	FEV1/VC max	TLC (L)	TLC (%)	RV (L)	RV (%)
15/05/2015	0.86	56.1	45.31	4.49	125.3	2.59	170.8
22/11/2018	1.37	93.9	52.98	4.77	133.2	2.18	139.8

FEV1: forced expiratory volume in the first second; VC max: maximal vital capacity; TLC: total lung capacity; RV: residual volume.

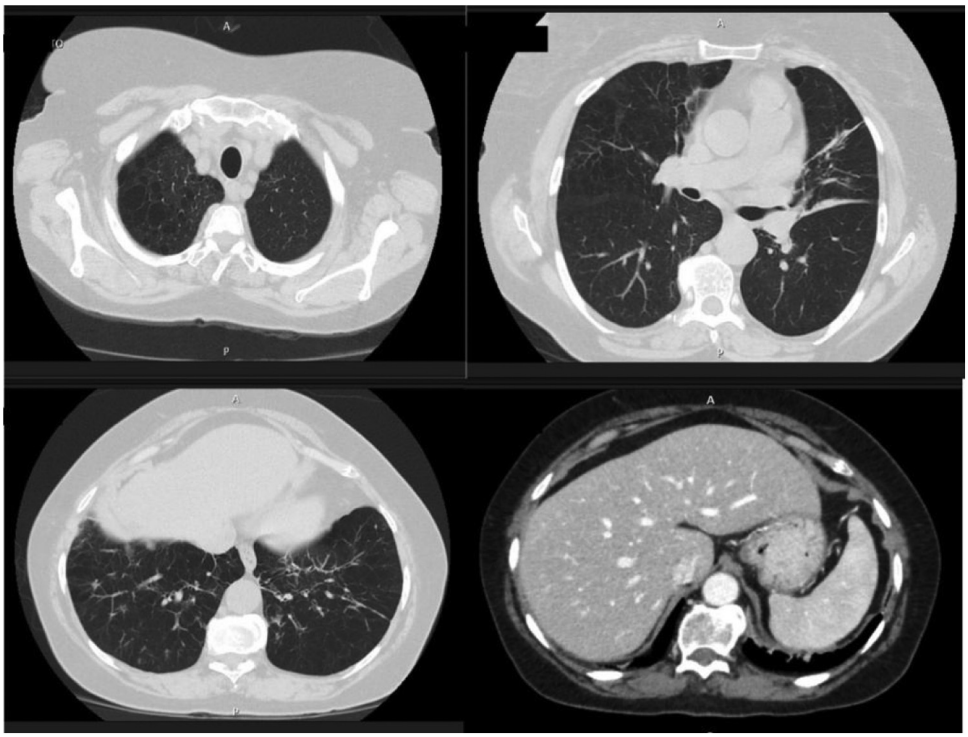


Figure 1 Thoracic CT scan showing emphysema in upper lobes and bronchiectasis in both inferior lobes. No abnormal findings were identified on abdominal CT scan: liver has standard size and regular edges.

diagnosis of AATD was inconsistent with serum levels, a sample was sent to an informal reference center in Portugal (IPATIMUP). This reevaluation comprised AAT phenotyping by isoelectric focusing, genotyping of four polymorphic sites including S and Z mutations and sequencing of *SERPINA1* coding region.[9] Only then was a conclusive result achieved, which revealed Mmalton homozygosity (p.Phe52del in a M2 allele) as the cause of AATD. At that time, the patient already presented signs of airway obstruction in lung function tests (Table 1). Given that she had been a former smoker for more than six months she began AAT augmentation therapy in August of 2015.

Respiratory complications became less frequent once AAT augmentation therapy started. Still, the patient had on average two exacerbations per year of an infectious nature with a total of seven hospitalizations in four years. After achieving a diagnosis of AATD the patient underwent a chest tomography scan to evaluate the extension of lung disease. This revealed bilateral bronchiectasis, mostly in basal regions, and centrilobular and paraseptal emphysema, mainly in superior lobes (Fig. 1).

Liver disease associated to AATD was also assessed by FibroScan® (measurement of liver stiffness to estimate liver scarring), which revealed a liver stiffness value of 7.9 kPa. A score that is compatible with significant fibrosis in the absence of liver cirrhosis.[18]

This work reports a case of a Portuguese patient diagnosed with two rare diseases: CVID and AATD. This case supports the findings of other authors, confirming the synergetic effect of both conditions on lung disease, leading to the appearance of bronchiectasis. This was well-established by Peppers et al.,[19] who found a strong relationship between unresolved or worsened bronchiectasis and lower levels of AAT, and resolved or improved bronchiectasis and higher levels of AAT, when submitting patients with immunodeficiencies under gammaglobulin infusions to serial chest CT scans. The pool of immunodeficient patients selected in their research had a higher prevalence of AAT mutations than the general population, establishing that the determination of the AAT phenotype in these patients is warranted.

In our patient, whereas CVID (by increasing patient susceptibility to pulmonary infections) is likely to have prompted a protease release by inflammatory cells (neutrophils and macrophages), it was AATD impaired anti-elastase activity that probably facilitated alterations in lung structures. Consistently, another previous study comprising

a total of 43 patients with CVID in which five were found to have AATD, also suggested an additive effect of these disorders into pulmonary illness.[17]

Despite so few reports of patients combining CVID and AATD, some studies have attempted to physically correlate these disorders: one of them, performed in 1983, failed to detect any evidence of linkage between these conditions in a family where hypogammaglobulinemia and AATD were found to segregate.[16] Interestingly, *SERPINA1* encoding AAT is located in chromosome 14 approximately 11 Mb apart from a cluster of immunoglobulin genes (*IGHG1-3* among others), which could explain in some rare cases a co-segregation of these disorders. However, a genetic screening of CVID was not performed in this case due to its low impact on patient follow up as well as it potential high costs to healthcare system.[13]

In result of the CVID and AATD joint diagnosis, this patient is currently undergoing two replacement therapies with subcutaneous immunoglobulin and endovenous human AAT. Here, it is important to stress that AAT infusion contains small amounts of IgA. This obligates a careful administration of AATD therapy in patients with IgA deficiency since they present a greater risk of adverse anaphylactic reactions due to the pre-existence of IgA antibodies. The Portuguese consensus document for AATD management actually discourages augmentation therapy in patients with IgA deficiency,[20] but so far this patient has been successfully treated with no record of side effects. Furthermore, lung functions tests of this patient have shown a remarkable increase in forced expiratory volume in one second (FEV1) after three years of AAT therapy. Although this phenomenon has not been described before, we believe it might be explained by a combination of optimized inhaled bronchodilators and AAT therapies together with cigarette smoking cessation prior to treatment in 2015 and inter-operator dependent differences in test execution and by the variability in the capacity of performance of the tests by the patient. On the other hand, the finding of liver fibrosis as confirmed by FibroScan® assessment were in accordance with previous studies of Mmalton patients (homozygous and/or heterozygous) showing that this allele is associated with hepatic accumulation of AAT and subsequently with liver disease, being to some degree a functional equivalent to a Z allele.[21]

Even though we could not rule out a genetic linkage between CVID and AATD in this case, we provide evidence that these might be somehow correlated with observed clinical features of lung disease. This report also emphasizes the singularity of combining two uncommon replacement therapies in controlling the worse outcomes of CVID (recurrent exacerbations) and AATD (severe airflow obstruction).

Conflict of interests

The authors declare no conflict of interests.

Acknowledgements

N. Martins would like to thank the Portuguese Foundation for Science and Technology (FCT-Portugal) for the Strategic project ref. UID/BIM/04293/2013 and ''NORTE2020 – Northern Regional Operational Program'' (NORTE-01-0145-FEDER-000012). IPATIMUP integrates the i3S Research Unit, which is partially supported by the Portuguese Foundation for Science and Technology (FCT; projects PEstC/SAU/LA0003/2013 and POCI-01-0145-FEDER-007274) and by Programa Operacional Regional do Norte (ON.2 – O Novo Norte and Norte 2020), through FEDER funds under the Quadro de Referência Estratégico Nacional (QREN; projects NORTE-07-0162-FEDER-00018 and NORTE-070162-FEDER-000067, and NORTE-01-0145-FEDER-000029).

References

1. Seixas SA [PhD thesis] Analysis of genetic diversity patterns in three functionally relevant regions of the human genome: apolipoprotein E (APOE), alpha 1-antitrypsin (PI), Duffy Blood Group (FY). University of Porto; 2002.
2. Gupta R, Sridhara S, Wood J. A rare case of alpha 1-antitrypsin deficiency associated with hypogammaglobulinemia and recurrent pulmonary thrombosis. Ann Thorac Med. 2014;9:39.
3. Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravitlles M. Estimated numbers and prevalence of PI*S and PI*Z alleles of alpha1-antitrypsin deficiency in European countries. Eur Respir J. 2006;27:77–84.
4. de Serres FJ, Blanco I. Prevalence of α1-antitrypsin deficiency alleles PI*S and PI*Z worldwide and effective screening for each of the five phenotypic classes PI*MS, PI*MZ, PI*SS, PI*SZ, and PI*ZZ: a comprehensive review. Ther Adv Respir Dis. 2012;6:277–95.
5. Blanco I, Bueno P, Diego I, Pérez-Holanda S, Lara B, Casas-Maldonado F, et al. Alpha-1 antitrypsin Pi*SZ genotype: estimated prevalence and number of SZ subjects worldwide. Int J Chron Obstruct Pulmon Dis. 2017;8:1683–94.
6. Stoller JK, Lacbawan FL, Aboussouan LS. In: University of Washington, editor. Alpha-1 antitrypsin deficiency. Summary. Diagnosis. Suggestive findings. Seattle: U.S. National Library of Medicine; 2019. p. 1–27.
7. Lara B, Martínez-Delgado B, Torres ML, Marín-Arguedas S, Bustamantee A, Miravitlles M. Alpha-1-antitrypsin deficiency associated with the mattawa variant. Arch Bronconeumol. 2016;52:617–8.
8. Rodriguez-Frias F, Miravitlles M, Vidal R, Camos S, Jardi R. Rare alpha-1-antitrypsin variants: are they really so rare? Ther Adv Respir Dis. 2012;6:79–85.
9. Silva D, Oliveira MJ, Guimarães M, Lima R, Gomes S, Seixas S. Alpha-1-antitrypsin (SERPINA1) mutation spectrum: three novel variants and haplotype characterization of rare deficiency alleles identified in Portugal. Respir Med. 2016;116:8–18.
10. Meira L, Boaventura R, Seixas S, Sucena M. Alpha-1 antitrypsin deficiency detection in a portuguese population. COPD J Chronic Obstr Pulm Dis. 2018;15:4–9.
11. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34–48.
12. Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Dräger R, et al. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol. 2003;4:261–8.
13. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract [Internet]. 2016;4:38–59. Available from: http://www.elsevier.com/journals/the-journal-of-allergy-and-clinical-immunology-in-practice/2213-2198%0Ahttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=607686990

14. U.S. National Library of Medicine. Common variable immune deficiency. Genetics home reference; 2019. p. p1–8.
15. Phung ND, Kubo RT, Spector SL. Alpha1-antitrypsin deficiency and common variable. Hypogammaglobulinemia in a patient with asthma. Chest. 1982;81:112–5.
16. Phung ND, Harbeck RJ, Helbling-Muntges C. Familial hypogammaglobulinemia: genetic linkage with alpha1-antitrypsin deficiency. Arch Intern Med. 1983;143:575–7.
17. Sansom ME, Ferry BL, Sherrell ZPMC, Chapel HM. A preliminary assessment of alpha-1 antitrypsin S and Z deficiency allele frequencies in common variable immunodeficiency patients with and without bronchiectasis. Clin Exp Immunol. 2002;130:489–94.
18. Pereira V, Gaspar R, Simões C, Maia L, Costa D, Carvão J, et al. Role of alpha-1 antitrypsin genotypes in the progression of adult liver disease. J Hepatol. 2018;68:S605–842.
19. Peppers BP, Zacharias J, Michaud CR, Frith JA, Varma P, Henning M, et al. Association between α_1-antitrypsin and bronchiectasis in patients with humoral immunodeficiency receiving gammaglobulin infusions. Ann Allergy Asthma Immunol. 2018;120:200–6, http://dx.doi.org/10.1016/j.anai.2017.11.014.
20. Lopes AP, Mineiro MA, Costa F, Gomes J, Santos C, Antunes C, et al. Portuguese consensus document for the management of alpha-1-antitrypsin deficiency. Pulmonology. 2018;24 Suppl. 1:1–21.
21. Spínola C, Bruges-Armas J, Pereira C, Brehm A, Spínola H. Alpha-1-antitrypsin deficiency in Madeira (Portugal): the highest prevalence in the world. Respir Med. 2009;103:1498–502.

C.S. Sousa[a,*], V. Teixeira[a], V. Pereira[b], R.B. Pinheiro[a], S. Seixas[c,d], N. Martins[c,e,f]

[a] *Pulmonology Department, Hospital Central do Funchal, Portugal*
[b] *Gastroenterology Department, Hospital Central do Funchal, Portugal*
[c] *Instituto de Investigação e Inovação em Saúde, Universidade do Porto (i3S), Porto, Portugal*
[d] *Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto, Portugal*
[e] *Faculty of Medicine, University of Porto, Portugal*
[f] *Pulmonology Department, Centro Hospitalar Universitário de São João, Portugal*

* Corresponding author.
E-mail address: claudiasabinafsousa@gmail.com (C.S. Sousa).

https://doi.org/10.1016/j.pulmoe.2020.04.016

Pulmonary intravascular lymphoma mimicking hypersensitivity pneumonitis

Santos et al. have recently characterized hypersensitivity pneumonitis (HP).[1] HP is diagnosed based on the patient's exposure history, physical examination (dyspnea, cough, and fever) findings, chest high-resolution computed tomography (HRCT) findings, and bronchoalveolar lavage (BAL). Santos et al. reported that most patients with HP exhibit respiratory symptoms (dyspnea and cough); and ground-glass opacification (GGO) occurred in thoracic CT of 76.7% acute and 91.7% subacute HP cases. HRCT features, including centrilobular diffuse nodules, ground-glass opacification (GGO), and mosaic attenuation, are especially useful for diagnosis.[1,2] Although these typical CT patterns are often useful in clinical practice, sometimes, they may also be present in other diseases. Through our recent clinical experience, we wish to highlight a pulmonary intravascular lymphoma with diffuse centrilobular GGO mimicking HP.

A 61-year-old man with no medical history who was a non-smoker and took no medications was admitted to our hospital with fever (38.5 °C), dyspnea, and cough. He had hypoxemia (SpO_2 88% at room air) but no crackles. He did not present with extrapulmonary symptoms. Blood tests revealed high C-reactive protein (4.2 mg/dL), lactate dehydrogenase (LDH) (923 U/L), and soluble interleukin-2 receptor (sIL-2R) (609 U/mL) levels. Serological tests for anti-neutrophil cytoplasmic antibody and other known autoantibodies against specific antigens were all negative. Chest HRCT revealed diffuse centrilobular GGO and nodules in the bilateral lungs (Fig. 1A). We initially suspected HP based on the respiratory symptoms, CT findings, and history of a dusty air conditioner at the patient's workplace. Although he was observed carefully without receiving steroid therapy to avoid antigens, his symptoms worsened; his LDH and sIL-2R levels increased. We could not perform BAL because of hypoxemia. Histological examination of a transbronchial lung biopsy (TBLB) specimen showed abnormal lymphocytes in the intravascular space of the capillaries (Fig. 1B). Immunohistochemical staining revealed that the tumor cells were positive for vascular antigens, including CD20, CD79α, and Ki-67 (Fig. 1C–E). Based on these findings, we diagnosed pulmonary intravascular large B-cell lymphoma (IVLBCL). Thereafter, he received chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone. His symptoms improved, and the diffuse opacities mostly disappeared.

IVLBCL is a rare extranodal subtype of non-Hodgkins lymphoma characterized by the selective growth of malignant lymphocytes within the blood vessels, especially in the capillaries, small arteries, and veins.[3] The clinical manifestation of pulmonary IVLBCL is nonspecific, and symptoms include fever, cough, and dyspnea.[4] The appearance on chest HRCT is varied and can include centrilobular nodules, GGO, and interlobular septal thickening.[5] Centrilobular nodules reflect lesions in the bronchioles located at the center of the pulmonary lobules, bronchial arterioles, broad interstitium, and lung parenchyma. In the present case, abnormal lymphocytes had infiltrated the capillary vessels and surrounding space, suggesting that small blood vessels in centrilobular structures can be significantly damaged by intravascular lymphoma. Consequently, we

Table 1 Previous case reports of pulmonary intravascular large B cell lymphoma diagnosed by transbronchial lung biopsy.

No.	Age	Sex	Symptoms	LDH (IU/L)	sIL2R (U/L)	CT imaging	Treatment	Outcome
1	82	Male	Forgetfulness	3040	1263	GGO	R-CHOP	Improvement
2	58	Female	Fever, weight loss	Unknown	6774	Normal findings	Unknown	Unknown
3	60	Female	Dyspnea, fever	1434	Unknown	GGO, nodules	Unknown	Death
4	69	Female	Dyspnea, fever, cough	1095	Unknown	GGO, interlobular septal thickening	CHOP	Unknown
5	69	Female	Fatigue, fever, dyspnea	1475	2771	Normal findings	Unknown	Unknown
6	62	Male	Dyspnea	1482	1570	Nodules	R-CHOP	Complete remission
7	57	Male	Fever, dyspnea	Unknown	Unknown	Haziness	Unknown	Unknown
8	85	Male	Dyspnea	829	2000	GGO	R-CHOP	Improvement
9	59	Male	Fever, dyspnea	605	2320	GGO, interlobular septal thickening	R-CHOP	Improvement
10	35	Female	Cough, dyspnea, fever	1554	Unknown	Consolidation, GGO	R-CHOP	Death
11	46	Male	Cough, fever	765	19100	Nodules, granular shadows	R-CHOP	Complete remission
12	71	Female	Fever	Unknown	Unknown	Normal findings	R-CHOP	Partial response
13	84	Male	Dyspnea	1120	2238	Normal findings	R-CHOP	Complete remission
14	61	Male	Night sweats, dyspnea	698	4130	Normal findings	R-CHOP	Complete remission
15	58	Female	Cough, fever	570	3699	Normal findings	R-CHOP	Improvement
16	39	Male	Dyspnea, fever	2214	1950	Normal findings	R-CHOP	Improvement
17	50	Female	Fever, anorexia, oedema, muscular pain	3386	6499	Normal findings	R-CHOP	Complete remission
18	65	Male	Fever, dyspnea	1625	2105	Interstitial shadows	CHOP	Complete remission
19	73	Male	Fever, dyspnea, skin lesions	1248	5290	Interstitial shadows	CHOP	Complete remission
20	49	Female	Fever, cough	5938	Unknown	Interstitial shadows	Cisplatin, cytarabine, dexamethasone	Improvement
21	65	Male	Dyspnea, dementia	2327	1820	Consolidation, bronchovascular bundles thickening	CHOP	Improvement
22	63	Male	Dyspnea, cough, fever, weight loss	1825	Unknown	Mosaic attenuations	CHOP	Complete remission

References:
1. Kaito S et al. Am J Case Rep. 2019, 2. Yamasaki M et al. Intern Med. 2018, 3. Zhang Y et al. Oncol Lett. 2018, 4. Zhang Y et al. Oncol Lett. 2018, 5. Nada T et al. J Gen Fam Med. 2017, 6. Takeshige T et al. Intern Med. 2017, 7. Wu F et al. Clin Nucl Med. 2016, 8. Yamakawa H et al. Intern Med. 2015, 9. Nishizawa T et al. BMJ Case Rep. 2014, 10. Chen Y et al. J Thorac Dis. 2014, 11. Sekiguchi Y et al. Int J Clin Exp Pathol. 2014, 12. Wagner T et al. Cancer Imaging. 2012, 13. Nakazato T et al. Ann Hematol. 2012, 14. Niida T et al. J Med Case Rep. 2011, 15. Kaku N et al. Intern Med. 2010, 16. Kotake T et al. Intern Med. 2010, 17. Kitanaka A et al. Hematol Oncol. 2009, 18. Asada N et al. Mayo Clin Proc. 2007, 19. Asada N et al. Mayo Clin Proc. 2007, 20. Goh SG et al. Pathology. 2002, 21. Kawamura T et al. Jpn J Clin Oncol. 2001, 22. Walls JG et al. Chest. 1999.

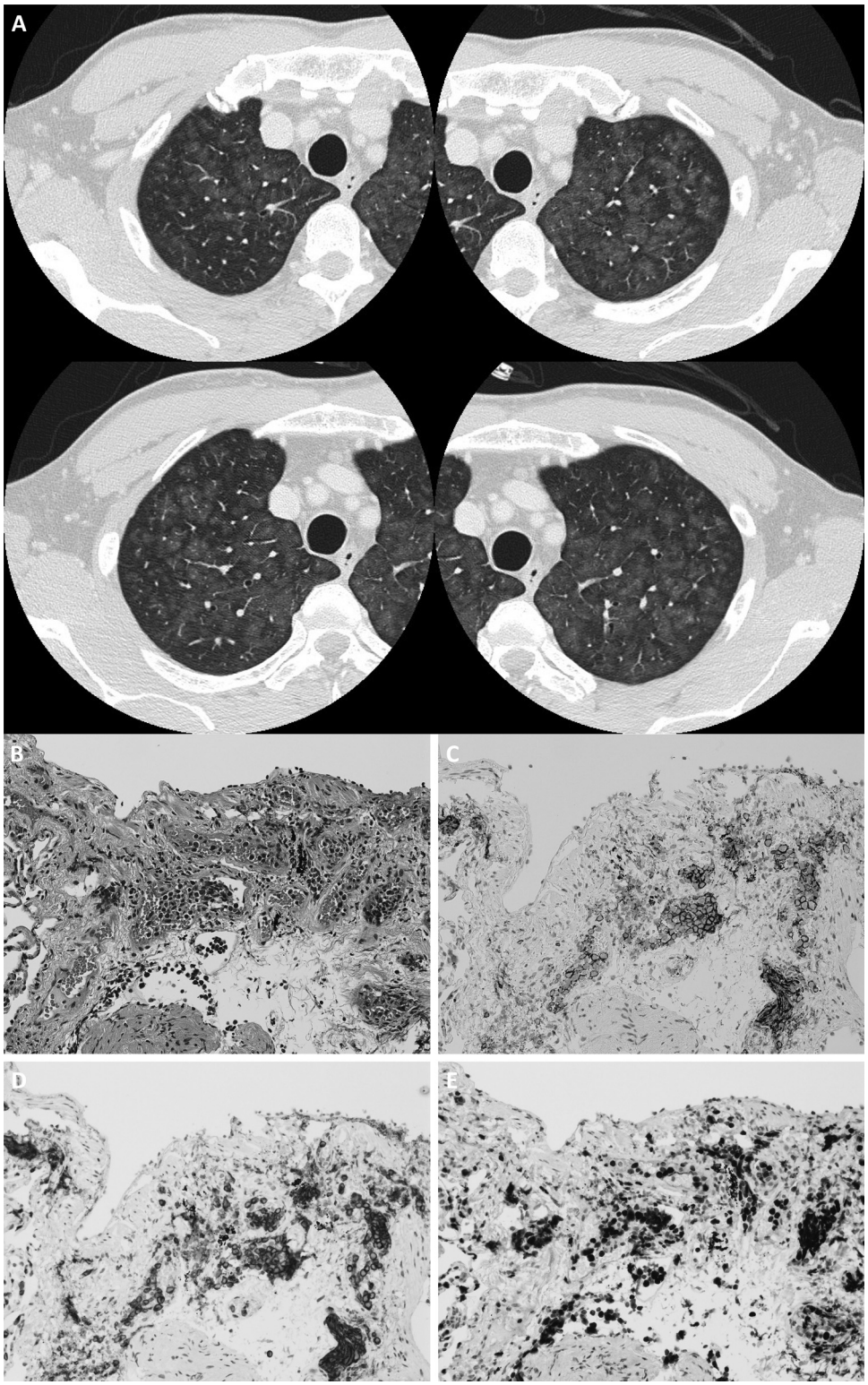


Figure 1 (A) Chest high-resolution computed tomography revealing diffuse ground glass opacities and nodules with centrilobular augmentation in the bilateral lungs. (B) Microphotographs of the transbronchial lung biopsy specimen. Atypical lymphocytes are seen in the intravascular space of capillary blood vessels. Immunochemical staining revealing that these cells were positive for CD20 (C), CD79α (D), and Ki-67 (E).

considered that HRCT revealed HP-like pale GGO and nodules with a centrilobular distribution pattern. It is probable that the resulting occlusive proliferation of tumor cells in the vascular lumens led to multiple minor infarctions, which manifested as coughing, dyspnea, and fever.

IVLBCL is often not identified during the lifetime, is only diagnosed at autopsy. To the best of our knowledge, only 22 cases, diagnosed by TBLB, have been reported during the past 20 years (Table 1). Respiratory symptoms including dyspnea and cough were present in 18 of those 22 cases, and both LDH and sIL2-R were elevated. Thoracic CT revealed GGO and nodules in some cases but was normal in others, and the response to treatment was mostly good. Based on these findings, TBLB may assist with diagnosis in patients complaining chiefly of respiratory symptoms, and early diagnosis may contribute to improved prognosis. TBLB may also be valuable in the differential diagnosis of other diseases, including HP (particularly acute/subacute HP).

Although the diagnosis of pulmonary IVLBCL is difficult due to its nonspecific clinical manifestation, in cases of diffuse centrilobular GGO and nodules on chest HRCT, it is necessary to consider not only HP but also pulmonary IVLBCL. Moreover, increased serum LDH and sIL-2R levels should suggest a diagnosis of IVLBCL, and TBLB be performed to make a definitive diagnosis.

References

1. Santos V, Martins N, Sousa C, Jacob M, Padrão E, Melo N, et al. Hypersensitivity pneumonitis: main features characterization in a Portuguese cohort. Pulmonology. 2020;26:130–7, http://dx.doi.org/10.1016/j.pulmoe.2019.09.004. Epub ahead of print.
2. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respir Crit Care Med. 2017;196:680–9.
3. Ponzoni M, Ferreri AJ, Campo E, Facchetti F, Mazzucchelli L, Yoshino T, et al. Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. J Clin Oncol. 2007;25:3168–73.
4. Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, et al. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol. 2004;127:173–83.
5. Cha MJ, Lee KS, Hwang HS, Kim TJ, Kim TS, Kim BT, et al. Pulmonary intravascular lymphomatosis: clinical, CT, and PET findings, correlation of CT and pathologic results, and survival outcome. Radiology. 2016;280:602–10.

R. Kikuchi[a,*], M. Ishiwari[a], H. Takoi[a], Y. Kono[a], A. Yoshimura[b], S. Abe[a]

[a] *Department of Respiratory Medicine, Tokyo Medical University Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan*
[b] *Department of Clinical Oncology, Tokyo Medical University Hospital, Tokyo, Japan*

* Corresponding author.
E-mail address: reo1129@tokyo-med.ac.jp (R. Kikuchi).

https://doi.org/10.1016/j.pulmoe.2020.03.008

Poly-resistant tuberculosis outbreak in Northern Portugal: a nine year tale

In 2017, the notification rate of tuberculosis in the Northern Region of Portugal was 21.1 cases per 100 000 inhabitants.[1] According to the National Tuberculosis Programme Surveillance System (SVIG-TB), poly-resistance to isoniazid and streptomycin (PR-HS) represented 2.6–5% of the cases notified in the Northern Region between 2009 and 2017 Although they represent a relatively low proportion of cases in Portugal, poly-resistances such as PR-HS are precursors to multidrug resistance and, consequently, should be closely monitored.[2]

Seventeen cases of pulmonary tuberculosis (TB) with PR-HS were recorded during 2009–2015 in Santa Maria da Feira (SMF), a municipality with 139 312 inhabitants (National Statistics Institute 2011) that belongs to Entre-Douro-e-Vouga-I community health centre cluster (EDVI). This represented a total of 9.3% of the TB notifications in EDVI in this period and was consistently higher than expected in the region (4.1%).

The existence of a cluster of 17 cases with an identical profile of antibacterial resistance led to the generation of the hypothesis of an ongoing TB outbreak. One epidemiological link had been established between two cases, but the remaining cases were apparently not associated. Research was carried out in order to confirm the existence of the outbreak.

Epidemiological surveys performed at the time of notification of PR-HS diagnosed cases from 2009 to 2015 were reviewed by the local Public Health Unit. Cases (or their closest relative alive) were re-interviewed, including clarification of social and occupational history in the two years prior to diagnosis. Specimens of culture-positive cases were sent to the National Mycobacteria Reference Laboratory (INSA) for strain genotyping, using Mycobacterial Interspersed Repetitive Units-Variable Number of Tandem Repeats method (MIRU-VNTR).

All 17 cases included were new cases. Eleven were male (64.7%), with a median age of 50 years (IQR: 22) at the time of diagnosis. All cases had pulmonary involvement, 82.4% were cavitated and 47.1% had positive sputum smear microscopy.

At the time of diagnosis, all cases were resident in SMF. Considering residence and occupation, the review of epidemiological information and the collection of new data made it possible to identify three contiguous parishes (Fig. 1) corresponding to place of residence or work in nine cases (53%).

Figure 1 Entre Douro e Vouga I municipalities — Arouca and Santa Maria da Feira: parishes according to occupation and residence of cases of poly-resistance to isoniazid and streptomycin in 2009 and 2018. Arrifana, Escapães and Milheirós de Poiares had a connection with 60% of the total cases.

A median of six people per case were identified for contact tracing (IQR: 3). No cases of active disease were detected and, out of the 146 contacts screened, 12 individuals were diagnosed with latent tuberculosis infection (8.2%). In 15 of the cases only cohabitants were screened, whereas in the other two cases screening involved 22 and 24 contacts at the workplace. No common frequency of social establishments was established.

Two additional epidemiological links were established — two neighbours and two social acquaintances (Fig. 2). Based on the three identified epidemiological links, five specimens were sent to INSA, for analysis through MIRU-VNTR. The five strains had an identical MIRU result, belonging to the Haarlem family.

Three additional HS poly-resistant cases were detected in 2016–2017. All cases belonged to the same previously identified risk area and had an identical MIRU profile. No epidemiological links between these cases were detected nor between these cases and the previous ones. In 2018 and 2019 no new HS poly-resistant cases were reported.

The initial contact investigation failed to identify two epidemiological links that were subsequently confirmed. However, 20–40% of the cases paired by genotyping were not identified during epidemiological investigations,[3] either due to insufficient epidemiological investigation or due to the inability/reluctance of patients to identify close contacts.

Lack of routine genotyping hinders the detection of links between cases that have no apparent epidemiological association and consequently the control of community transmission.[4] In this instance, the high prevalence of PR-HS should have triggered further investigation at an earlier stage. The proportion of latent tuberculosis infections was also below the threshold expected (up to 15% in the Portuguese population), supporting the hypothesis of unsuccessful contact identification.[5]

The strain identified belongs to the Haarlem family which is more prevalent in Europe, Central America and the Caribbean, with a known association to resistance and outbreaks.[6] So far, there is no knowledge of identical strains in nearby areas, although similar resistance phenotypes in cases not epidemiologically linked were detected in 2011–2013 in bordering parishes — unavailable strains or different genotypic profiles.

Although only eight out of 20 cases reported from 2009 to 2017 in EDVI were genotyped, one has a reasonable degree of suspicion that all cases could belong to the same transmission chain. At this point, two years have elapsed since the last notified case, the most likely period of progression to active disease since a contact with an infectious case.[7]

Retrospective analysis strongly supports the existence of a long transmission chain of poly-resistant TB in EDVI, partially confirmed by genotyping. The added value of genotyping of specific strains allows the follow-up of disease control and the pinpointing of shortcomings of epidemiological investigations.

Conflicts of interest

The authors have no conflicts of interest to declare.

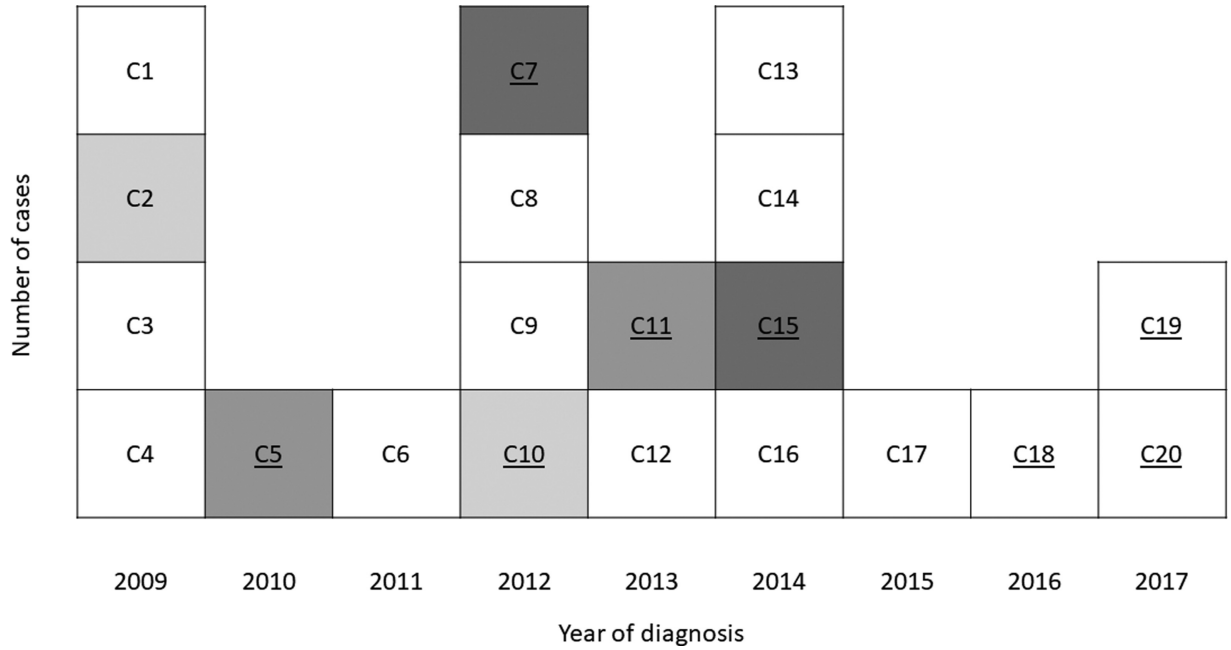


Figure 2 Temporal distribution of poly-resistant cases of tuberculosis in Entre Douro e Vouga I. Only cases underlined were genotyped — all had the same genotype (according to MIRU-VNTR method). Epidemiological links (C2–C10, C5–C11, C7–C15) are matched by color.

CRediT authorship contribution statement

B. Gomes: Conceptualization, Investigation, Writing - original draft. **G. Molina-Correa:** Investigation. **L. Neves-Reina:** Investigation. **A.C. Oliveira:** Investigation, Supervision. **R. Macedo** Methodology. **C. Carvalho:** Validation, Writing review & editing. **A.M. Correia:** Validation, Writing review & editing.

References

1. C. Carvalho, A.L. Rodrigues, B. Gomes, M. Gomes. Tuberculose na Região de Saúde do Norte (2017). Departamento de Saúde Pública, Administração de Saúde da Região de Saúde do Norte, I.P, 2020 [To be published oficial report].
2. Manson AL, Cohen KA, Abeel T, Desjardins CA, Armstrong DT, Barry CE III, et al. Genomic analysis of globally diverse Mycobacterium tuberculosis strains provides insights into the emergence and spread of multidrug resistance. Nat Genet. 2017;49:395–402, http://dx.doi.org/10.1038/ng.3767.
3. National Tuberculosis Controllers Association. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR: Recommend Rep. 2005;54(RR-15):1.
4. David S. Utilização estratégica da genotipagem do Mycobacterium tuberculosis no controlo da tuberculose. Rev Port Pneumol (English Ed). 2008;14(4):509–16, http://dx.doi.org/10.1016/S2173-5115(08)70278-1.
5. Lopes JS, Rodrigues P, Pinho ST, Andrade RF, Duarte R, Gomes MGM. Interpreting measures of tuberculosis transmission: a case study on the Portuguese population. BMC Infect Dis. 2014;14(1):340, http://dx.doi.org/10.1186/1471-2334-14-340.
6. Cubillos-Ruiz A, Sandoval A, Ritacco V, López B, Robledo J, Correa N, et al. Genomic signatures of the haarlem lineage of Mycobacterium tuberculosis: implications of strain genetic variation in drug and vaccine development. J Clin Microbiol. 2010;48(10):3614–23, http://dx.doi.org/10.1128/JCM.00157-10.
7. Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. Bmj. 2018;362, http://dx.doi.org/10.1136/bmj.k2738.

B. Gomes[a,b,c,*], G. Molina-Correa[a], L. Neves-Reina[a], A.C. Oliveira[a], R. Macedo[d], C. Carvalho[b,e], A.M. Correia[b]

[a] *Entre Douro e Vouga I Public Health Unit, Northern Regional Health Administration, Santa Maria da Feira, Portugal*
[b] *Department of Public Health, Northern Regional Health Administration, Porto, Portugal*
[c] *Instituto de Saúde Pública da Universidade do Porto, EPIUnit, Porto, Portugal*
[d] *Head of the National Reference Laboratory for Mycobacteria, National Institute of Health Dr. Ricardo Jorge, Lisbon, Portugal*
[e] *Multidisciplinary Unit for Biomedical Research (UMIB), Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal*

* Corresponding author.
E-mail address: bgomes@arsnorte.min-saude.pt (B. Gomes).

29 January 2020

https://doi.org/10.1016/j.pulmoe.2020.02.006

Unusual effectiveness of systemic steroids in Whipple disease

To the Editor,

Whipple's disease is a rare disorder caused by the Gram-positive bacterium Tropheryma whipplei (TW), formerly known as Tropheryma whippelii, that localizes initially in the lamina propria of small bowel with prominent gastrointestinal symptoms and weight loss.[1] However, it can also cause a wide range of clinical manifestations, due to its spreading to other sites (i.e. endocardium, lymph nodes, central neurologic system, serum membranes)[2] including pulmonary manifestations.[3,4]

We draw here to attention a quite unique case of Whipple disease complicated by lung involvement probably due to an immune reconstitution syndrome.

This refers to a caucasian 77-year-old man diagnosed with Whipple's disease in 2015 (relapsed in 2018) treated with doxycycline and hydroxychloroquine then withheld because of gastrointestinal intolerance. In the past medical history, he was diagnosed with a type 1 myelomonocytic chronic leukemia, peripheral axonal neuropathy, dermatitis due to a possible immune reconstitution syndrome, osteoporosis due to steroid therapy treated with vertebroplasty, hypertension, aortic insufficiency, bilateral glaucoma, benign prostatic hypertrophy and intestinal-type gastric adenocarcinoma treated with endoscopic resection in 2019.

He was admitted on September 2019 to the emergency room due to high fever the night before, thoracalgia and arterial blood gases abnormalities (pO2 58 mmHg, pCO2 29 mmHg, pH 7.45); chest X-ray documented lung involvement with pleural effusion (Fig. 1). Vital parameters indicated mild hypotension (90/50 mmHg), tachycardia (115 bpm), tachypnoea (30/min), no alteration in body temperature. Blood tests showed anemia (6.8 g/dl) mild elevation of C-Reactive Protein (2.8 mg/dl), increased white cells (40.130 mmc), Pro-calcitonin (34 pg/ml), and creatinine (1.6 mg/dl), while D-dimer was inconsistent and cardiac enzymes were negative. The patient was transferred to our ward on oxygen (2 L/min flow by nasal prongs), drug regimen with piperacillin/tazobactam and prophylactic low molecular weight heparin was started, blood transfusion was also performed. Due to clinical signs of malabsorption, parenteral nutrition was instituted.

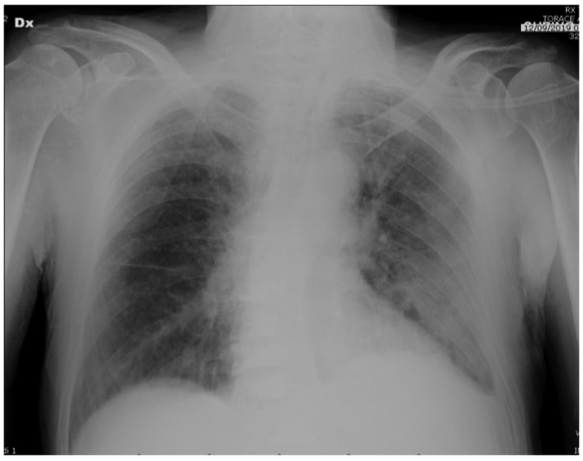


Figure 1 Chest-X-Ray at admission in emergency room showing left lung parenchymal consolidation and ipsilateral pleural effusion.

Chest ultrasound confirmed a bilateral pleural effusion, larger on the left, with extended B-lines. Bilateral apical opacities appeared at the chest-CT (Fig. 2 upper panels). The whole body exams performed to search for the most common pathogens (bacteria and respiratory viruses) were negative, and the bronchiolo-alveolar lavage also showed no significant isolates.

Following an initial clinical improvement, the patient condition deteriorated with fever, tachypnea and worsening of arterial hypoxemia (pO2 40 mmHg with 2 L/min oxygen) and impending fatigue of the respiratory system. Ceftazidime was added, taking the history of TW disease into account. A second chest-CT documented the worsening of the lung involvement (Fig. 2 lower panels) so patient was transferred to our respiratory intensive care unit, oxygen supplementation was set up to FiO2 50% and antibiotic regimen with cephalosporin was started.

The decision to perform trans-bronchial biopsies of the lung parenchymal consolidations with rigid bronchoscope was thus taken with patient under sedation after intubation; histology is reported in Fig. 3. After the procedure, a steroid therapy with 1.5 mg/kg of methylprednisolone was started and a rapid clinical improvement with a parallel resolution of the respiratory failure was observed over the following days. In agreement with the infectious diseases consultant, the therapy with doxycycline and hydroxychloroquine was started. Finally, the patient was discharged without any oxygen supplementation and steroid therapy was prolonged and gradually tapered during follow-up.

The clinical manifestation of Whipple's disease involving lung parenchyma in our patient follows other very rare cases in the past literature.[4] As for the other manifestations involving different sites,[2] diagnosis is confirmed at the biopsy stain both by finding the pathogen with PCR method and with the PAS positivity.[1]

However, the case here reported was atypical: first, we did not find PCR positivity for TW in the biopsy (despite the PAS positivity); second, patient clinically improved once systemic steroid therapy was instituted, although steroids are not a cornerstone of disease treatment.[5] Indeed, since then, patient continued to deteriorate and lung infiltrates continued to worsen despite antibiotic treatment with cephalosporins, an effective first-line therapy in severe Whipple's disease.[1]

In the clinical history of this patient we have found that he had a dermatological manifestation probably caused by an immune reconstitution syndrome after starting the therapy for Whipple's disease. The immune reconstitution syndrome in Whipple disease is extremely rare but reported in the literature[6] with a positive PAS staining, but negative PCR for TW, probably due to the previous clearance of the pathogen with antibiotic therapy.[7] That was exactly what happened in our patient with lung involvement. Probably, steroid therapy might have played a role in limiting immune reconstitution. In addition, due to his hematological pathology, this patient was exposed to another risk of a immune-mediated complication i.e. the alteration of the monocytes function connected to an abnormal phagocytosis

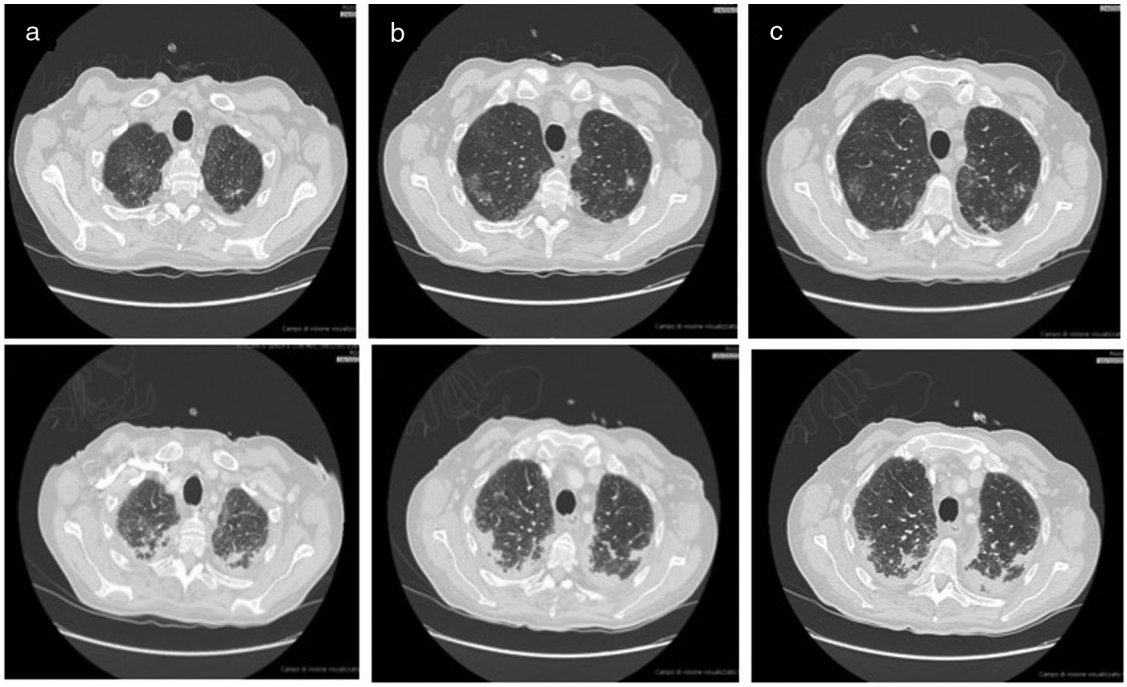


Figure 2 The first chest-CT performed in the ward demonstrated bilateral lung opacities with the appearance of ground-glass in the upper lobes (*see upper panel 1 in different slices a to c*).The second chest-CT performed after patient's worsening demonstrated progression of the lung parenchimal opacities, with consolidations and reticolo-nodular interstitial thickening (*see lower panel 2 in different slices a to c*).

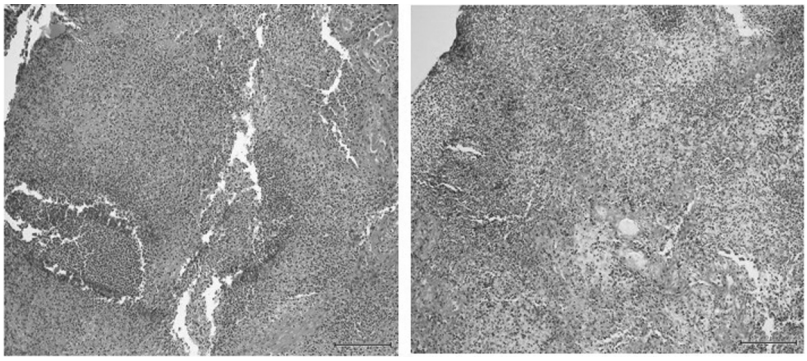


Figure 3 Histologic specimen shows a non-caseating granulomatous inflammation (*left panel*); the PAS-stain was positive (*right panel*) but the PCR detection for Tropheryma whipplei was negative.

and proliferation of TW.[8] The fluctuation in the number of white blood cells that we observed during admission could have led to the development of an aberrant response to antibiotics and the elimination of the pathogen.[6] At discharge, specific therapy for Whipple's disease was continued because of the risk of relapse, of worsening when systemic steroids or other immunosuppressants are administered, and of manifestations due to the immune reconstitution when steroid therapy is suspended rapidly.[1]

To the best of our knowledge, this specific manifestation involving the lung has not been previously described and it sheds light on whether steroid therapy could be added in some cases of Whipple's disease to avoid the risk of further complications, such as immune-reconstitution syndrome.

Funding

The authors declare that no funding was received for this paper.

Consent to publish data

Informed consent to publish data was obtained by the patient.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

We want to thank Professional Editor Colin Woodham for language editing.

References

1. Fenollar F, Lagier JC, Raoult D. Tropheryma whipplei and Whipple's disease. J Infect. 2014;69:103–12.
2. Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic tropheryma whipplei: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. Medicine (Baltimore). 2010;89:337–45.
3. Kelly CA, Egan M, Rawlinson J. Whipple's disease presenting with lung involvement. Thorax. 1996;51:343–4.
4. Urbanski G, et al. Whipple disease revealed by lung involvement: a case report and literature review. Chest. 2012;141:1595–8.
5. Mahnel R, et al. Immunosuppressive therapy in Whipple's disease patients is associated with the appearance of gastrointestinal manifestations. Am J Gastroenterol. 2005;100:1167–73.
6. Moos V, et al. Immunopathology of immune reconstitution inflammatory syndrome in Whipple's Disease. J Immunol. 2013;190:2354–61.
7. Feurle GE, et al. The immune reconstitution inflammatory syndrome in Whipple disease: a cohort study. Ann. Intern. Med. 2010;153:710–7.
8. Marth T, Neurath M, Cuccherini BA, Strober W. Defects of monocyte interleukin 12 production and humoral immunity in Whipple's disease. Gastroenterology. 1997;113:442–8.

M. Fontana[a], S. Cerri[a], G. Bernardelli[b], L. Brugioni[c], E. Clini[a,*], R. Tonelli[a,d]

[a] *University Hospital of Modena, Respiratory Diseases Unit, Department of Medical and Surgical Sciences, University of Modena Reggio Emilia, Italy*
[b] *University Hospital of Modena, Pathologic Anatomy Unit, Modena, Italy*
[c] *University Hospital of Modena, Internal and Emergency Medicine Unit, Modena, Italy*
[d] *Clinical and Experimental Medicine PhD Program, University of Modena Reggio Emilia, Italy*

* Corresponding author at: University of Modena and Reggio Emilia, Chair of Respiratory Medicine, Director Post-doctoral School in Respiratory Medicine, Azienda Ospedaliera-Universitaria di Modena, Policlinico, Director, Pneumology Unit, Largo del Pozzo 71, 41125 Modena, Italy.
E-mail address: enrico.clini@unimore.it (E. Clini).

8 February 2020

https://doi.org/10.1016/j.pulmoe.2020.02.007

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Pneumocystosis pneumonia in immunocompromised patients

Dear Editor,

We read the publication on ''Pneumocystosis pneumonia: A comparison study between HIV and non-HIV immunocompromised patients'' with a great interest.[1] Rego de Figueiredo et al. reported that ''*non-HIV patients had worse outcomes with higher incidence of invasive mechanical ventilation.*''[1] Pneumocystosis pneumonia is an important infection that can be seen in an immunocompromised host, regardless of HIV serological status. General practitioners usually recognize pneumocystosis pneumonia as an important complication in HIV - infected patients. The worse clinical outcome in non-HIV patientsmight be due to delayed or under diagnosis. According to a recent report by Li et al.,[2] a delay between admission and starting antimicrobial therapy was common and a longer delay time period was observed in non-HIV infected cases.[3] In addition, specific guidelines for management and prophylaxis of pneumocystosis pneumonia in non-HIV immunocompromised patient are seldom mentioned.[3,4] Practitioners should recognize and include of pneumocystosis pneumonia in the differential diagnosis of pneumonia in any immunocompromised host regardless of HIV serostatus.

Ethical disclosure

No conflict of interest.

No funding.

The work is a letter to editor and requires no ethical committee approval or written informed consent.

Both authors equally contribute and approve for the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

References

1. Rego de Figueiredo I, Vieira Alves R, Drummond Borges D, Torres M, Lourenço F, Antunes AM, et al. Pneumocystosis pneumonia: a comparison study between HIV and non-HIV immunocompromised patients. Pulmonology. 2019;25(5):271–4.
2. Li MC, Lee NY, Lee CC, Lee HC, Chang CM, Ko WC. Pneumocystis jiroveci pneumonia in immunocompromised patients: delayed diagnosis and poor outcomes in non-HIV-infected individuals. J Microbiol Immunol Infect. 2014;47(1):42–7.
3. Salzer HJF, Schäfer G, Hoenigl M, Günther G, Hoffmann C, Kalsdorf B, et al. Clinical, diagnostic, and treatment disparities between HIV-infected and non-HIV-infected immunocompromised patients with pneumocystis jirovecii pneumonia. Respiration. 2018;96(1):52–65.
4. Avino LJ, Naylor SM, Roecker AM. Pneumocystis jirovecii Pneumonia in the Non-HIV-Infected Population. Ann Pharmacother. 2016;50(8):673–9.

Beuy Joob[a,*]

[a] *Sanitation 1 Medical Academic Center, Bangkok, Thailand*

Viroj Wiwanitkit[b]

[b] *Honorary professor, dr DY Patil University, Pune, India*

[*] Corresponding author.
E-mail address: beuyjoob@hotmail.com (B. Joob).

21 October 2019
Available online 17 November 2019

https://doi.org/10.1016/j.pulmoe.2019.10.005

PULMONOLOGY

www.journalpulmonology.org

COMMENT

"Book Commentary: Donner CF, Ambrosino N, Goldstein RS. Pulmonary Rehabilitation, 2nd Edition. CRC Press Pub. Pp 518."

Andrew Ries

Departments of Medicine and Family Medicine and Public Health, University of California, San Diego, CA, USA

The second edition of Pulmonary Rehabilitation edited by Donner, Ambrosino, and Goldstein is a welcome, timely, and comprehensive reference that draws upon an international roster of experts and rising stars in pulmonary rehabilitation. The book will prove to be an excellence source of information for both practitioners and investigators with extensive documentation and timely references focused on new reports since publication of the first edition in 2005. Topics span the past, present, and future horizons of this rapidly emerging field, and are particularly relevant to the transformational changes in the world and in healthcare resulting from the COVID-19 pandemic. Chapters document not only the practice and benefits of well-established programs for patients with chronic obstructive pulmonary disease (COPD) but also cover the growing usefulness of pulmonary rehabilitation principles in conditions and diseases beyond COPD and to settings beyond traditional hospital and center-based programs. These include: 1) conditions such as neuromuscular disorders, interstitial lung diseases, cystic fibrosis, and bronchiectasis; 2) the usefulness of pulmonary rehabilitation as adjunctive therapy to surgical procedures such as lung transplantation and lung volume reduction surgery; and 3) the use of pulmonary rehabilitation in the intensive care unit and inpatients hospitalized with exacerbations of underlying chronic lung diseases. Of particular interest in the COVID-19 era that seriously compromised traditional outpatient programs is the discussion of new approaches to expand the reach of pulmonary rehabilitation to the home and via the potential use of telerehabilitation, and even a timely chapter on pulmonary rehabilitation in patients recovering from COVID-19. Finally, there are chapters reviewing several new and innovative rehabilitation tools such as noninvasive ventilation, whole-body vibration training, and neuromuscular electrical stimulation. Overall, this book is well worthwhile as a reference for current pulmonary rehabilitation practices as well as for new ideas and horizons in this rapidly emerging field.

E-mail address: aries@health.ucsd.edu

https://doi.org/10.1016/j.pulmoe.2020.08.004