Pulmonology Journal

volume 26 / number 2 / March/April 2020

PULMONOLOGY JOURNAL

Previously **Revista Portuguesa de Pneumologia**

volume 26 / number 2 / March/April 2020

Editorials

Original articles

ISSN 2531-0437

www.journalpulmonology.org

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

volume 26 / number 2 / March/April 2020

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

Zurbano, 76, 4° Izq.
28010 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 2. March-April 2020

CONTENTS

Letters to the Editor

Correspondance

Breaking news

Pulmonol. 2020;**26(2)**:61–62

PULMONOLOGY

www.journalpulmonology.org

EDITORIAL

Monoclonal antibodies for chronic obstructive pulmonary disease

Recently, monoclonal antibodies have been used for the treatment of various severe diseases, such as rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, cancer infections among others. They have immunomodulatory effects, are prepared against specific cytokines, inhibit specific enzymes or signaling molecules. Today, more than 60 monoclonal antibodies have been approved for clinical therapeutic use.[1] Monoclonal antibodies are generally well tolerated, but those that suppress the immune system may reactivate latent infections, such as tuberculosis or hepatitis B.[1]

In pulmonary diseases, monoclonal antibodies have been tested primarily in asthma with significant results.[2] The anti-IgE and the anti-interleukin-5 (IL-5) antibodies are now part of the regular treatment of severe asthma.[3] The anti-IL-5 antibodies had been shown to be very effective in severe eosinophilic asthma.[2]

These findings led to the hypothesis that these antibodies could be also effective in the sub-group of COPD patients with high eosinophilic counts in the blood. Thereafter, two monoclonal antibodies (Mepolizumab, Benralizumab), both against IL-5 have been tested in eosinophilic COPD patients.

In 2017 Pavord et al. performed two randomized, placebo-controlled, double-blind, parallel-group trials of Mepolizumab (METREY and METREO).[4] One hundred mg in METREX and 100 or 300mg in METREO of Mepolizumab were given to an eosinophilic phenotype of COPD patients (>150 per cubic millimeter). The primary end point in both trials was the annual rate of moderate or severe exacerbations. It was concluded that Mepolizumab at a dose of 100 mg was associated with lower annual rate of exacerbations than placebo. In addition it was shown that the greatest effect was found among patients with higher blood eosinophilic counts.[4]

In 2019 Fernadez Romero et al.[5] reviewed the literature of the clinical efficacy, safety and side effects of Mepolizumab in the management of eosinophilic COPD patients and concluded that out of the three trials only one study showed significant effect on the annual rate of exacerbations.[5] In addition, Condreay et al.[6] analysed in more detail the results of the METREX and METREO studies in order to identify genetic variants associated with the efficacy of Mepolizumab. This post-hoc analysis failed to identify genetic effects on Mepolizumab-treatment response.[6]

More recently, the results of another monoclonal antibody, Benralizumab, for the prevention of COPD exacerbations were published.[7] Benralizumab, an IL-5 receptor alpha-directed monoclonal antibody was tested in two trials (GALATHEA and TERRANOVA) in patients with eosinophilic COPD (>220 per cubic millimeter). Various doses of benralizumab were used vs placebo with primary end point the annual exacerbations. The study showed that at 56 weeks, none of the COPD exacerbation rate for any dose reached significance vs placebo.[7]

Basing the treatment on the number of eosinophils in the blood could be the wrong hypothesis, since there is no strong evidence that they reflect the number and the function of the eosinophils in the lung tissue. Tumor necrosis factor (TNF) inhibitors were shown to be effective in a small subgroup of severe asthma patients but were ineffective in COPD, although they showed same effect among patients with COPD and rheumatoid arthritis.[8]

It is obvious that there are very few studies of monoclonal antibodies in COPD with controversial results for anti IL-5 or TNF-alpha and this may be because the pathogenesis of COPD at the cellular and molecular level is extremely complex.[9] A large number of phenotypic pathways, involving the immune system, with even larger number of endotypes have been identified as playing a role in COPD. Thus, a single monoclonal antibody cannot be effective on all pathways and this may reflect that there is no dominant role for any single cytokine or chemokine in COPD.[10] Better understanding of the pathogenesis of COPD at the cellular, molecular, genetic and immune levels may lead to more targeted use of monoclonal antibodies in restricted groups of patients with COPD with specific endotypes. Although, monoclonal antibodies could be the future of personalized treatment in COPD, there is a long way to go before they became part of everyday practice in COPD.

https://doi.org/10.1016/j.pulmoe.2019.11.002

Conflicts of interest

No conflict of interest to declare

References

1. Maris JD. Overview of therapeutic monoclonal antibodies. www.uptodate.com. Accessed Oct 3rd, 2019.
2. Bel EH, Ten Brinke A. New Anti-Eosinophil drugs for asthma and COPD: targeting the trait. Chest. 2017;152(6):1276–82.
3. Tzortzaki EG, Georgiou A, Kampas D, Lemessios M, Markatos M, Adamidi T, et al. Long-term omalizumab treatment in severe allergic asthma: the South-Eastern mediterrenian ''real life'' experience. Pulm Pharmacol Ther. 2012;25(1):77–82.
4. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med. 2017;377(17):1613–29.
5. Fernadez Romero GA, Beros J, Criner G. Mepolizumab for the prevention of COPD exacerbations. Expert Rev Respir Med. 2019;13(2):125–32.
6. Condreay LD, Gao C, Bradford E, Yancey SW, Ghosh S. No genetic associations with mepolizumab efficacy in COPD exacerbations with peripheral blood eosinophilia. Resp Med. 2019;155: 26–8.
7. Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D, et al. GALATHEA Study Investigators; TERRANOVA Study Investigators. Benralizumab for the prevention of COPD exacerbations. N Engl J Med. 2019;381(11):1023–34.
8. Matera MG, Calzetta L, Cazzola M. TNF-alpha inhibitors in asthma and COPD: we must not throw the baby out with the bath water. Pulm Pharmacol Ther. 2010;23(2):121–8.
9. Tzortzaki EG, Papi A, Neofytou E, Soulitzis N, Siafakas N. Immune and genetic mechanisms in COPD: possible targets for therapeutic interventions. Curr Drug Targets. 2013;14(2):141–8.
10. Matera MG, Page C, Rogliani P, Calzetta L, Cazzola M. Therapeutic monoclonal antibodies for the treatment of COPD. Drugs. 2016;76(13):1257–70.

Nikolaos Siafakas
Department of Thoracic Medicine, University of Crete, Medical School, Boutes, Heraklion, Crete, Greece
E-mail address: siafakan@uoc.gr

15 November 2019
Available online 10 December 2019

Pulmonol. 2020;**26(2)**:63–65

PULMONOLOGY

www.journalpulmonology.org

EDITORIAL

Is adherence to treatment influenced by the ability to use inhaled devices in patients with COPD correctly?

Chronic Obstructive Pulmonary Disease (COPD) is a frequent and disabling disease, and it is responsible for important limitations in daily life and high economic impact on the health system.[1] Patients with moderate to severe COPD are affected by chronic symptoms, poor quality of life and frequent exacerbations, and are at high risk of mortality for respiratory and non respiratory diseases.[2] Pharmacologic treatment, based mainly on bronchodilators and inhaled corticosteroids, is able to modify several outcomes of the disease, although a clear demonstration of the possibility of improving survival is still lacking.[3,4] Unfortunately, the adherence to the long-term use of inhaled drugs is very low, thereby reducing the impact of the pharmacologic treatment on the progression of the disease. While adherence in the randomised clinical trials is high, several observational data from real life have documented that a variable percentage of between 30 and 50% of patients with COPD use regularly inhaled drugs.[5,6]

Several factors have been associated with a poor adherence, some of them related to demographic characteristics such as age and gender, clinical aspects of the disease (severity, comorbidities), socio-economic factors (education, health literacy, social/familiar support, income), characteristics of the inhaled therapy (dose regimen, number and type of inhalers, satisfaction with inhalers), satisfaction with drug efficacy and clinician expertise.[5] In real life, most severe patients have a better adherence to treatment than patients with mild to moderate disease, probably due to the greater limitation in daily life and to the perception of the efficacy of the treatment.

In this issue of Pulmonology, Duarte-de-Araujo and coworkers[7] extended a previous recent observation[8] on a fairly large group of patients with COPD of different severity: they used a specific psychometric tool (Measure of Treatment Adherence), validated for the Portuguese population in 2001, consisting of seven questions leading to a total score ranging from 6 to 42. They demonstrated that 16.5% of the patients examined were classified as non-adherent, and that this percentage was significantly higher in less severe COPD patients. Furthermore, a significant relationship was found between non adherence and FEV1%, also when data were corrected in a logistic analysis by several confounding factors. This relationship may be expected, because the severity of symptoms may promote a more regular use of the inhaled drugs, confirming the positive effect of the pharmacologic treatment. This observation is not new, although the several observational studies in this topic area have not clearly underlined this specific point. In effect, in the usual current clinical practice, low adherence to treatment both in asthma and in COPD is more frequent in less severe patients who do not understand the need for a continuous regular treatment when they only have mild symptoms and limitations. In any case, low adherence to the pharmacologic treatment has been demonstrated to be associated with poor outcomes of the disease, such as increased frequency and severity of symptoms and exacerbations, progressive decline in pulmonary function and even mortality.[9]

A second point considered in the paper[7] is the relationship between performance in using inhalers and adherence to treatment. The authors used a clearly defined checklist for the major critical errors according to the different dry-powder inhalers (DPI), and they found that almost 40% of the patients misused the recommended inhalers; this was lower with DPIs than with metered dose inhalers (MDIs). In a multivariate analysis, misuse of inhalers was only significantly associated with age, gender, and socio-economic level, while no significant relationship was observed between inhaler technique and adherence to medications. This topic has been extensively reported in the literature: several observational studies showed the high prevalence of incorrect use of the inhalers in both asthma and COPD patients, and that this fact was associated with an inadequate control of the disease in many countries, including Italy and Portugal.[10,11] In a recent large survey including almost 3000 patients with COPD selected by the general practitioners (GPs) or pulmonary specialists, more than 50% of the patients made one or more critical errors in the use of different devices, more frequently using MDIs and soft-mist inhalers[12]; the rate of severe COPD exacerbations was twice

https://doi.org/10.1016/j.pulmoe.2020.01.005

greater in patients with poor inhaler technique in comparison with the others.

Correctly using the inhaler devices is crucial for a good result of the therapy, independently of a possible but not clearly demonstrated effect on drug compliance. Some general recommendations should be remembered: (a) if possible, avoid the use of different devices with a single patient, in order for them to have to learn only one inhalation technique; we have now different drugs and combinations (ICS/LABA or LABA/LAMA or ICS/LABA/LAMA) administered with the same device, allowing movement from one combination to another based on the clinical assessment, without changing the inhalation technique; it has been already demonstrated that switching from one device to another, if not accompanied by appropriate training for the patient, can be associated with poor clinical outcomes and increased use of health care resources[13]; (b) monotherapy with a single inhaler, possibly administered once daily, has been reported to be more effective in the control of the disease that multiple devices used at different time of the day[14]; (c) education on the use of inhalers and practical demonstrations of the inhalation technique at each visit is crucial in order to have a correct interpretation of the results of the pharmacologic treatment. Recently new ''intelligent'' devices have been developed, to simplify the inhalation technique (like new breath-actuated MDIs)[15] or to check for the correct inhalation technique and adherence.[16,17] On the other hand, the contribution of the inhaler misuse to general adherence to the maintenance therapy is still controversial, as suggested by some authors[18] but not confirmed by the paper from Duarte-de-Araujo et al.[7]

The final point of the manuscript by Duarte-de-Araujo et al.[7] is related to the adherence of GPs to the recommendations derived from international guidelines or documents, like the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines. As reported in previous surveys,[19,20] overtreatment is the most frequent situation, with less severe patients receiving frequently regular ICS where there is reduced use of bronchodilators. This fact has some historical reasons (ICS/LABA combinations were the first drugs showing a positive effect on many clinical and functional outcomes of COPD) and it is related to prescription feasibility (in some countries, like Italy for example, more recent LABA/LAMA combinations may only be prescribed by pulmonary specialists) and also to the lack of appropriate clinical assessment of the patients. This tendency to overtreat COPD patients has not greatly changed in recent years despite the wide diffusion of GOLD guidelines, which suggests that in real life many physicians believe that in a disease poorly responsive to pharmacologic treatment, it is better to use all available drugs independently of the baseline disease severity, in order to try to prevent the progressive deterioration of the disease.

In summary, we have several demonstrations that in the last 10 years adherence to inhaled therapy is very poor in COPD patients, and the paper from Duarte-de-Araujo et al.[7] confirms this assumption. There are several determinants of this poor adherence, and this paper adds to the many factors also the level of disease severity as assessed by FEV1. In any case, all potential determinants may together only explain a minor part of the total variance, suggesting that other personal factors may have a strong influence on adherence to treatment. As an example, the adherence to the prescribed therapy is strongly influenced by the individual patient's general behaviour and personality, and it may be independent of the real efficacy of the drugs, as demonstrated by the post-hoc analysis of the TORCH study[21] where adherence was associated to a reduction in mortality and in hospital admissions due to severe exacerbations independently of the specific treatment arm, including the placebo arm. Strategies for implementing and reinforcing adherence should be promoted, although the efficacy of these intervention has not been definitely proven.[5,22]

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016;21:14–23.
2. Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), update 2019, http://goldcopd.com.
3. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775–89.
4. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-Daily Single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378:1671–80.
5. López-Campos JL, Quintana Gallego E, Carrasco Hernández L. Status of and strategies for improving adherence to COPD treatment. Int J Chron Obstruct Pulmon Dis. 2019;14:1503–15.
6. Ingebrigtsen TS, Marott JL, Nordestgaard BG, Lange P, Hallas J, Dahl M, et al. Low use and adherence to maintenance medication in chronic obstructive pulmonary disease in the general population. J Gen Intern Med. 2015;30:51–9.
7. Duarte-de-Araújo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: analysing factors associated with a successful treatment. Pulmonology. 2019;pii: S2531-0437(19):30121–7. Jun 17.
8. Duarte-de-Araújo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: understanding patients' adherence to inhaled medications. Int J Chron Obstruct Pulmon Dis. 2018;13:2767–73.
9. Mäkelä MJ, Backer V, Hedegaard M, Larsson K. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107:1481–90.
10. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011;105:930–8.
11. Maricoto T, Rodrigues LV, Teixeira G, Valente C, Andrade L, Saraiva A. Assessment of inhalation technique in clinical and functional control of asthma and chronic obstructive pulmonary disease. Acta Med Port. 2015;28:702–7.
12. Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A. Chronic obstructive pulmonary disease exacerbations and inhaler handling: real-life assessment of 2935 patients. Eur Respir J. 2017;49, pii. 1601794.
13. Braido F, Lavorini F, Blasi F, Baiardini I, Canonica GW. Switching treatments in COPD: implications for costs and treatment adherence. Int J Chron Obstruct Pulmon Dis. 2015;10:2601–8.
14. Vestbo J, Leather D, Diar Bakerly N, New J, Gibson JM, Salford Study Investigators. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. N Engl J Med. 2016;375:1253–60.
15. Usmani O, Roche N, Marshall J, Danagher H, Price D. An innovative corticosteroid/long-acting β2-agonist breath-

triggered inhaler: facilitating lung delivery of fluticasone propionate/formoterol fumarate for the treatment of asthma. Expert Opin Drug Deliv. 2019;16:1367–80.
16. Carpenter DM, Roberts CA, Sage AJ George J, Horne R. A review of electronic devices to assess inhaler technique. Curr Allergy Asthma Rep. 2017;17:17.
17. Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. Eur Respir J. 2018;51, pii: 1701126.
18. Braido F, Chrystyn H, Baiardini I, Bosnic-Anticevich S, van der Molen T, Dandurand RJ, et al. ''Trying, But Failing'' - the role of inhaler technique and mode of delivery in respiratory medication adherence. J Allergy Clin Immunol Pract. 2016;4:823–32.
19. Corrado A, Rossi A. How far is real life from COPD therapy guidelines? An Italian observational study. Respir Med. 2012;106:989–97.
20. Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. Int J Chron Obstruct Pulmon Dis. 2015;10:2207–17.
21. Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax. 2009;64:939–43.
22. Vanhaecht K, Lodewijckx C, Sermeus W, Decramer M, Deneckere S, Leigheb F, et al. Impact of a care pathway for COPD on adherence to guidelines and hospital readmission: a cluster randomized trial. Int J Chron Obstruct Pulmon Dis. 2016;11:2897–908.

Manuela Latorre[a,b], Giulia Parri[a], Pierluigi Paggiaro[a,*]
[a] *Department of Surgery, Medicine, Molecular Biology and Critical Care, University of Pisa, Italy*
[b] *Pulmonary Unit, Nuovo Ospedale Apuano, Massa, Italy*

[*] Corresponding author.
E-mail addresses: manuela.latorre@yahoo.it (M. Latorre), giuliaparri@gmail.com (G. Parri), pierluigi.paggiaro@unipi.it (P. Paggiaro).

7 January 2020
Available online 6 February 2020

Pulmonol. 2020;**26(2)**:66–72

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

COPD: Analysing factors associated with a successful treatment

A. Duarte-de-Araújo[a,b,c,*], **P. Teixeira**[a,b], **V. Hespanhol**[d,e], **J. Correia-de-Sousa**[a,b,f]

[a] *Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal*
[b] *ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal*
[c] *Respiratory Department, H. Sª Oliveira, Guimarães, Portugal*
[d] *Department of Pneumology, Centro Hospitalar de S. João, Porto, Portugal*
[e] *Faculty of Medicine (FMUP), University of Porto, Portugal*
[f] *Horizonte Family Health Unit, Matosinhos, Portugal*

Received 5 February 2019; accepted 23 May 2019
Available online 17 June 2019

KEYWORDS
COPD;
Inhalation technique;
Adherence;
Prescriber disagreement;
Clinical outcomes

Abstract
Objectives: To evaluate if non-adherence to inhaled medications, inhalers mishandling or the prescribers' non-adherence to GOLD strategy are associated with mMRC grade, CAT score, COPD acute exacerbations or FEV_1%.
Methods: A cross-sectional study on COPD was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães. Patients ≥40 years diagnosed according to GOLD criteria were recruited consecutively. A survey of demographic and clinical data was used. Adherence was assessed by using the Measure of Treatment Adherence (MTA) questionnaire. Inhalation technique was evaluated by using checklists of correct steps and critical errors, and inhalers' misuse was defined when one or more critical errors were made, whatever the number or types of inhalers in use. To evaluate the prescriber non-adherence to GOLD strategy, the patients' current medication was compared with therapeutic standards proposed by the GOLD 2017 strategy for the same ABCD groups. A statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
Results: We studied 303 participants, 79.5% males, mean age = 67.5 years. A total of 285 completed the MTA questionnaire. Non-adherence was referred by 47 (16.5%) patients, and a significant negative association was found between adherence and CAT score and FEV_1%. 285 patients performed 499 inhalations manoeuvres with 10 different IDs. Inhaler misuse was observed in 113 (39.6%) patients, and was not associated with CAT score, mMRC grade, ECOPD or FEV_1%. We found deviations from the GOLD strategy in 133 (44.3%) patients, which were negatively related to CAT score, mMRC grade and ECOPD.

* Corresponding author.
E-mail address: duartearaujodr@sapo.pt (A. Duarte-de-Araújo).

https://doi.org/10.1016/j.pulmoe.2019.05.012

Conclusions: In the present study we failed to prove a positive association between non-adherence to medication, inhalers mishandling or prescribers' non-adherence to GOLD strategy with symptoms, exacerbations and airflow limitation. Conversely, more symptomatic and more obstructed patients were more adherent to medication, previous ECOPD seems to improve prescribers' adherence to treatment guidelines, and symptoms, ECOPD and FEV_1% were not significantly associated with inhaler technique.

Background and objectives

Chronic Obstructive Pulmonary Disease (COPD) is the only leading cause of death with rising mortality and morbidity,[1] and currently represents one of the most significant health problems at international level. It is a chronic and incurable disease, but symptoms significantly improve with inhaled therapy, even though it is unlikely that most patients remain asymptomatic. Lung function also improves with medication, and acute exacerbations can be prevented or mitigated. Symptoms, acute exacerbations and airflow limitation are important treatment outcomes. Treatment can be described as successful if an appropriate change is measured in an appropriate outcome.[2] Some factors relying on patients, on health-care providers or on the physician–patient relationship can be significantly related to poor clinical outcomes. Some of them are common and modifiable. Non-adherence to medications in COPD has been related to mortality, poor disease control and poor quality of life. In the LASSYC study,[3] poor adherence was associated with more exacerbations. Vestbo et al., using data from the TORCH study, also found significant differences in survival and risk of severe exacerbations according to the degree of patient adherence.[4] Inhaled medication is the mainstay of COPD management. Inhaler misuse has been associated with increased rate of severe COPD exacerbations,[5] but the overall impact on clinical outcomes remains currently unknown. It would appear to be predictable that poor clinical outcomes is related to non-adherence to guidelines, but the relationship between adherence to guidelines and some clinical outcomes, such as the number of acute exacerbations, may be different than expected.[6,7]

The objective of this study was to assess whether non-adherence to inhaled medications, inhaler mishandling or prescriber non-adherence to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy are associated with medical Research Council Dyspnoea Questionnaire (mMRC) grade, COPD Assessment Test (CAT) score, COPD acute exacerbations and FEV_1%.

Methods

Study design and population

A cross-sectional study was conducted in the outpatient respiratory care of Hospital de Guimarães, Portugal, between March 2016 and May 2017. Stable patients over 40 years old and diagnosed as suffering from COPD according to the GOLD criteria were consecutively included, after having given their written informed consent. Exclusion criteria were the refusal to participate and the inability to understand simple questionnaires. The study was approved by the Hospital's Ethics Committee, the Research Ethics Committee of Minho University and the Portuguese Data Protection Agency. We followed the STROBE guidelines for reporting observational studies.[8]

Demographic and clinical characteristics

A questionnaire of demographic and clinical data was used. Symptoms were evaluated using the Portuguese versions of the CAT questionnaire and the mMRC scale. Results were later dichotomised according to GOLD thresholds for considering more or less symptomatic impact of COPD. A variable''symptoms'' was created and dichotomised into fewer symptoms (mMRC <2 and CAT <10) or more symptoms (mMRC $\geq$2 and/or CAT $\geq$10). The number of COPD acute exacerbations (ECOPD) registered in the previous year was evaluated. We defined ECOPD according to GOLD, as an acute worsening of respiratory symptoms that result in additional therapy,[9] but also requiring an unplanned medical visit, whatever the severity of symptoms. The number of ECOPD were also dichotomised according to GOLD as <2 exacerbations and $\geq$2 exacerbations or $\geq$1 hospitalisation. All participants performed spirometry according to the American Thoracic Society and the European Respiratory Society recommendations for standardised lung function testing,[10,11] and referenced according to Global Lung Function Initiative prediction equations (GLI 2012).[12] The diagnosis of ACO was not considered in the present

study, because neither its definition nor the clinical characteristics or diagnostic criteria are universally accepted, and they changed during the period the project was conceived and developed, and data was collected and interpreted.[13]

Adherence to medication

Adherence to inhaled medication was assessed using the Measure of Treatment Adherence (MTA), a psychometric tool validated for the Portuguese population in 2001, with a reported Cronbach's alpha of 0.74. It consists of a seven items questionnaire, reflecting common patterns of non-adherent behaviours. Answered on a 6-point Likert scale (with 1 = always, 2 = almost always, 3 = often, 4 = sometimes, 5 = rarely and 6 = never), points are summed, and total scores range from 6 to 42, with higher scores indicating higher self-reported adherence. Non-adherence was defined by a score $\leq$5, after dividing the total score by the number of questions. This cut-off was validated by the MTA authors.[14]

Inhaler technique

Inhaler technique was assessed using previously defined checklists developed according to the instructions provided by the manufactures and to previous literature,[15] and also including essential steps and critical errors (Table 1). Errors considered critical were related to priming/loading or the inhalation manoeuvre, and could substantially affect drug delivery to the lungs. These included lack of inhalation through the mouthpiece for all devices, slow and not forceful inhalation for dry powder inhalers (DPI) and rapid or forceful inhalation for pressurised metered-dose inhalers (pMDI) or soft-mist inhalers (SMI). Device-dependent critical errors are listed in Table 2.

Participants were invited to demonstrate the use of their prescribed inhaler devices, just as they do it at home, and the correct steps and critical errors were recorded. Inhaler misuse was defined when one or more critical errors were made, whatever the number or types of inhalers in use.

Adherence to guideline

The prescribers' adherence to GOLD 2017 strategy was assessed by comparing the patient's current medication with the therapeutic standards for the same ABCD groups. Current medication was evaluated using the hospital data base, the health data platform, or patient self-reported information. Patients were categorised as GOLD-concordant or GOLD-discordant based on criteria presented in Table 3.

Statistical analysis

The statistical association between dichotomous variables was assessed with the Chi-square test and intensity of linear association with the Pearson's correlation coefficient. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Table 1 Check-list of steps and critical errors.

1.Correct priming or loading (Incorrect priming or loading were considered critical error)
2.Exhalation before inhalation (No-exhalation before inhalation was not considered critical)
3.Correct inhalation (Incorrect inhalation were considered critical error)
4.Hold the breath a few seconds after inhalation (except when using a spacer) (Not holding the breath or exhalation through the mouthpiece was not considered critical)
5.Finalisation (clean the mouth-piece, remove used capsule after verifying that no powder remains, check colour changing in control window, close ID and wash the mouth if necessary)

Table 2 Critical errors in different IDs.

1. Aeroliser®, Breezhaler®, and Handihaler®: failure to insert the capsule, failure to press and release buttons, powder remaining in the capsule after inhalation.
2. Diskus®: failure to open the cover, to slide the lever until it clicks, or not keeping inhaler horizontally.
3. Ellipta®: failure to slide cover down until a click is heard or block air vent with fingers.
4. Genuair®: failure to remove the cap, to press and release the button until the control window has changed to green, not holding inhaler horizontally, and not changing control window to red after inhalation.
5. pMDI: failure to remove cap, not shaking the inhaler (suspensions only), not holding the inhaler in the upright position, poorly synchronised hand actuation and inhalation (except using a spacer), inhalation through the nose, actuation against teeth, lips or tongue.
6. Respimat®: lack of cartridge in the device, failure to open the cap, twisting the base or pressing the dose-release button, poorly synchronised hand actuation and inhalation.
7. Spiromax®: failure to hold the inhaler in upright position, failure to open mouthpiece cover until a click is heard or blocking air vent with fingers.
8. Turbuhaler®: failure to remove cover, to hold the inhaler upright when twisting the grip (tolerance $\pm 45^{\circ}$) until a click is heard.

Table 3 Type and number of deviations from the GOLD strategy.

Type of deviations	Number of deviations
1. Underuse	
1.1. Absence of medication (in B, C and D groups; in A group if symptoms or exacerbations)	3
1.2. Under-medication (under-therapeutic bronchodilation; only SAMA or SABA as need in B, C or D groups)	13
2. Overuse	
2.1. Doubling medication (2 or more different LAMA, LABA or ICS)	8
2.2. Overuse of bronchodilators (LABA + LAMA in A group)	34
2.3. Inhaled corticosteroids overuse (in A or B groups)	98
3. Inappropriate bronchodilation (only LABA in C or D groups)	1

Note: A total of 157 deviations from GOLD guideline were found in 133 patients: occasionally different deviations overlap in the same patient.

Results

Adherence to medication

A total of 303 COPD outpatients were included in the study. The most important demographic, clinical and functional characteristics of the patients are presented in Table 4.

A total of 285 participants completed the MTA questionnaire, and 47 (16.5%) were considered non-adherent to inhaled medications. The distribution of non-adherent patients were respectively 17.0%, 53.3%, 25.5% and 2.1% from GOLD I to IV ($p = 0.002$) and 34.0%, 36.2%, 4.3% and 25.5% from A to D of GOLD 2017 classification ($p = 0.53$). No association between adherence and mMRC score was found; an association between non-adherence and CAT score was found (26.5% of patients with CAT score <10 and 12.8% $\geq$10 were non-adherent, $p = 0.023$). A significant relationship was found between non-adherence and FEV_1% (the mean FEV_1% of non-adherent and adherent patients were respectively 62.3 and 49.9, $p < 0.001$). Non-adherence was respectively found in 19.3% and 12.4% of patients reporting <2 and $\geq$2 ECOPD, however without statistical significance ($p = 0.087$). When controlling for age, gender, education level, monthly income, Graffar classification, active smoking, symptoms and FEV_1%, FEV_1% was the only variable significantly associated with adherence (Table 5).

Inhaler technique

285 patients carried out 499 inhalations manoeuvres with 10 different IDs (Aeroliser®, Breezhaler®, Diskus®, Ellipta®, Genuair®, Handihaler®, pMDI, Respimat®, Spiromax® and Turbuhaler®) in a total of 66 (13.2%) pMDI, 128 (25.7%) single-dose inhalers (sDPI), 228 (50.8%) multiple dose inhalers (mDPI) and 77 (15.4%) SMI-Respimat®. Misuse due to critical errors was observed in 113 (39.6%) patients. It was significantly related to the type of inhaler device and was observed respectively in 53.6%, 28.4%, 26.2% and 24.2% demonstrations using a pMDI, SMI, mDPI or sDPI ($p < 0.001$). Neither was any statistically significant association found between inhaler misuse and CAT score, mMRC grade, FEV_1% and ECOPD. When controlling for age, gender, education level, monthly income, Graffar classification, active smoking, symptoms and FEV_1%, only age, gender and Graffar classification were significantly associated with inhaler technique (Table 5). There was also no statistical relationship

Table 4 Demographic, clinical and functional characteristics of COPD patients.

Characteristics	$n = 303$
Male gender	241 (79.5)
Mean age (years)	67.5 ± 10.2
Age $\geq$ 65 years	186 (61.4)
Very low education level $\leq$ 3 school years	89 (29.4)
Graffar social classification	
Graffar 1	2 (0.7)
Graffar 2	13 (4.3)
Graffar 3	106 (35.5)
Graffar 4	174 (58.2)
Graffar 5	4 (1.3)
Very low monthly income (<530 Euros)	197 (65.7)
Mean smoking amount (pack/years)	49.3 ± 32.4
mMRC grade $\geq$ 2	185 (61.1)
CAT score $\geq$ 10	152 (72.4)
Frequent ECOPD ($\geq$2/last year)	115 (38.0)
Post-bronchodilator mean FEV_1%	53.2 ± 19.7
GOLD stage	
I	30 (9.9)
II	127 (41.9)
III	106 (35.05)
IV	40 (13.2)
GOLD 2017 classification	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)

Note: Data shown as mean $\pm$ SD or *n* (%).
Abbreviations: mMRC, medical Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 5 Predictors of adherence and inhalers misuse.

Logistic regression – predictors of adherence									
		B	S.E.	Wald	df	Sig.	Exp(*B*)	95% C.I. for Exp(*B*)	
								Lower	Upper
Step 1	Symptoms 0/1	.499	.405	1.518	1	.218	1.648	.745	3.647
	Age	.022	.019	1.472	1	.225	1.023	.986	1.061
	Ed. level 0/1	.349	.466	.560	1	.454	1.417	.569	3.532
	Gender	−.386	.425	.825	1	.364	.680	.295	1.564
	Curr. smok.	−.715	.432	2.730	1	.098	.489	.210	1.142
	FEV_1%	−.029	.010	9.367	1	.002	.971	.953	.990
	Income 0/1	.248	.382	.423	1	.515	1.282	.607	2.708
	Graffar 0/1	−.179	.413	.188	1	.665	.836	.372	1.878
	Constant	1.371	1.608	.727	1	.394	3.940		
Logistic regression – predictors of inhalers misuse									
		B	S.E.	Wald	df	Sig.	Exp(*B*)	95% C.I. for Exp(*B*)	
								Lower	Upper
Step 1	Symptoms 0/1	.366	.343	1.139	1	.286	1.442	.736	2.827
	Age	.039	.015	6.811	1	.009	1.039	1.010	1.070
	Ed. level 0/1	.084	.341	.061	1	.806	1.088	.557	2.123
	Gender	.736	.325	5.132	1	.023	2.087	1.104	3.946
	Curr. smok.	.266	.370	.519	1	.471	1.305	.632	2.696
	FEV_1%	−.002	.007	.044	1	.833	.998	.984	1.013
	Income 0/1	.215	.290	.547	1	.460	1.239	.702	2.190
	Graffar 0/1	−.775	.318	5.951	1	.015	.461	.247	.859
	Constant	−3.272	1.271	6.632	1	.010	.038		

a. Variable(s) entered on step 1: Symptoms 0/1 (symptoms = 0: mMRC <2 and CAT <10; symptoms = 1: mMRC ≥2 and/or CAT ≥10), age, education level 0/1 (<4 years at school = 0; ≥4 years = 1), gender, current smoking 0/1, FEV_1%, monthly income 0/1 (<530 Euros = 0; ≥530 euros = 1), Graffar social classification 0/1 (4 and 5 = 0; 1,2 and 3 = 1).

between inhaler technique and adherence to medications ($p = 0.328$).

Adherence to guideline

We found deviations from the GOLD 2017 therapeutic strategy in 133 (44.3%) patients, and they are described in Table 3. The most frequent deviations were related to the overuse of inhaled corticosteroids in GOLD A and B groups and the overuse of bronchodilators in the A group. Overuse of ICS and/or bronchodilators accounted for 88% of total prescriber deviations. It should be noted here that during the period of patient recruitment the 2017 GOLD version was published and 24,4% of patients moved from C and D to A and B groups. In the historical context in which they were treated, medications now considered excessive, could then have been appropriate. Table 6 describes the type of prescriber lack of agreement by GOLD 2017 ABCD groups.

We found no association between deviations from the GOLD guideline and FEV_1. However, 78.8% of the patients medicated according to GOLD and 62.2% of those not according to GOLD had a CAT score ≥10 ($p = 0.023$), and 68.5% of patients medicated according to GOLD and 53.0% of those not according had an mMRC grade ≥2 ($p = 0.024$). 58.7% of those who were medicated according to GOLD and 12.8% of patients medicated not according to GOLD referred to frequent exacerbations in the previous year ($p < 0.001$).

Discussion

Patient non-adherence to medications, inhaler mishandling and prescriber disagreement to therapeutic standards are common and modifiable factors which are likely to be related to poor clinical outcomes. Lung function, symptoms and acute exacerbations are important clinical outcomes among COPD patients, and they were measured in the present study. We found a negative association between adherence and the clinical or functional severity of the disease. No significant association was found between inhaler misuse and ECOPD, symptoms or FEV_1%. Lack of agreement with the GOLD strategy was more frequent than poor-adherence to medication or inhaler misuse, and previous ECOPD seems to improve prescriber adherence to treatment guidelines.

In the present study, adherence was significantly related to the clinical and functional severity of the disease. Patients who complained of more symptoms or airflow limitation adhered better to inhaled medications. This may be due to the fact that patient adherence to medication is based on their perceptions of symptoms severity. A positive association between poor-adherence behaviours and

Table 6 Prescribers disagreement to GOLD 2017 strategy by ABCD groups.

	Group A	Group B	Group C	Group D
Guide-line concordant	26 (37.7)	44 (37.3)	5 (71.4)	92 (86.8)
Overuse	43 (62.3)	70 (59.3)	1 (14.3)	4 (3.8)
Underuse	0 (0)	4 (3.4)	0 (0)	10 (9.4)
Inadequate bronchodilator	0 (0)	0 (0)	1 (14.3)	0 (0)

Note: Results presented as number (%) of patients. $p < 0.001$; in 3 patients there was no information related to current medications.

poor treatment outcomes has been described in previous papers.[16,17] A previous study reported that patients are likely to alter the recommended medication based on how they feel,[18] and that the sentence ''I vary my recommended management based on how I am feeling'' was a significant predictor of non-adherence to medications.

We found inhaler mishandling disappointingly common but not related to patient clinical or functional characteristics. This is consistent with other published studies.[19,20] However, it was expectable a significant impact on clinical outcomes, such as symptoms and acute exacerbations. This is a surprising issue, and may be both because we have not analysed the specific medication affected by inhaler misuse and because of the substantial overuse of ICs and/or bronchodilators by a significant number of patients. In medical literature, a small number of studies report an association between critical errors and COPD outcomes.[21] In a recently published study the authors found inhaler misuse associated with an increased rate of severe COPD exacerbations,[22] and in two different cross-sectional studies inhaler misuse was related to increased risk of hospitalisation and emergency room visits.[23,24]

Prescribers not respecting guidelines was common in the present study and more frequent than poor-adherence or inhaler misuse, but there is currently no standard threshold of satisfactory adherence.[25] The most frequently found deviations were related to overuse of inhaled corticosteroids. This was to be expected because the diagnosis of ACO was not considered in the present study and the GOLD 2017 report was published while data was being collected, with many patients shifting from high to low risk groups. The overall non-adherence to GOLD guidelines seems to be very common, even though varying from country to country.[26] In previous studies, overuse of ICS was also the most common recorded deviation to international standards of therapy.[27,28] A previous published study found that exacerbations-related hospitalisations lead to improved adherence to GOLD guidelines.[6] In the present study, previous ECOPD seems to improve prescriber adherence to treatment guidelines, and patients medicated in non-agreement with the GOLD were less symptomatic and had fewer exacerbations. This is an intriguing issue, and can partly be due to fact that the present study did not control for features suggestive of airway hyperactivity. Moreover, because overuse of ICS and/or bronchodilators accounted for 88% of prescriber deviations, there were no reasons for patients medicated in non-agreement with guidelines to present more symptoms or more airflow limitation.

The present study draws attention to the choice of significant outcomes to evaluate responsiveness to treatment, and to the appropriate instruments to measure them.[29] Lung function, symptoms and acute exacerbations are important treatment outcomes in COPD. FEV_1 is a highly reproductive measurement strongly related to mortality. Dyspnoea is an important patient-centred outcome. However, it is very subjective, and the level of breathlessness depends on the level of patient activity. The mMRC scale, an instrument that has stood the test of time,[30] measures mainly dyspnoea-related disability, and, like other tools, may be not useful in evaluating responsiveness to treatment.[31] CAT has strong measurement properties in the overall impact of the disease, and the GOLD recommends its routine use in clinical practice. COPD exacerbations are the single most important feature of COPD, they indicate clinical instability and progression, and are related to increased mortality. It is an important outcome both from the physicians' and patients' perspectives. However, there is no standardised definition, and unreported exacerbations, not evaluated in the present study, have the same clinical relevance. A measure of self-reported adherence, the Test of the Adherence to Inhalers (TAI),[32] specifically designed to identify non-adherence to inhalers in asthma and COPD patients, is presently available in Portuguese-Brazilian language. To the best of our knowledge, MTA was the only validated instrument to measure adherence in the Portuguese language at the time patients were recruited for the present study. However, we acknowledge that factors related to adherence with inhaler therapy in COPD present some unusual features which makes the use of many unspecific questionnaires less appropriate.

Conclusions

In the present study, done in a real world context, we failed to prove a positive association between non-adherence to medication, inhaler mishandling or prescriber non-adherence to GOLD strategy with symptoms, exacerbations and airflow limitation. Conversely, more symptomatic and more obstructed patients adhered better to medication, previous ECOPD seems to have improved prescriber adherence to treatment guidelines, and symptoms, ECOPD and FEV_1% were not significantly associated with inhaler technique.

Financing

The authors have no financing to declare.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Sharif R, Cuevas C, Wang Y, Arora M, Sharma G. Guideline adherence in management of stable chronic obstructive pulmonary disease. Respir Med. 2013;107:1046–52.
2. Van Der Molen T, Pieters W, Bellamy D, Taylor R. Measuring the success of treatment for chronic obstructive pulmonary disease – patient, physician and healthcare payer perspectives. Respir Med. 2002;96:s17–21.
3. Montes de Oca M, Menezes A, Wehrmeister F, Lopez M, Casas A, Ugalde L, et al. Adherence to inhaled therapies of COPD patients from seven Latin American countries: the LASSYC study. PLoS One. 2017;12(11):e0186777.
4. Vestbo J, Andersen J, Calverley P, Celli B, Ferguson G, Jenkins C, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax. 2009;64:939–43.
5. Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A, et al. Chronic obstructive pulmonary disease exacerbations and inhaler handling: real-life assessment of 2935 patients. Eur Respir J. 2017;49:1601794.
6. Incalzi R, Corsonello A, Pedone C, Masotti G, Bellia V, Grassi V, et al. From Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines to current clinical practice: an overview of the pharmacological therapy of stable chronic obstructive pulmonary disease. Drugs Aging. 2006;23(5):411–20.
7. Miravitlles M, Sicras A, Crespo C, Cuesta M, Brosa M, Galera J, et al. Coasts of chronic obstructive pulmonary disease in relation to compliance with guidelines: a study in the primary care setting. Ther Adv Respir Dis. 2013;7(3):139–50.
8. von Elm E, Altman D, Egger M, Pocock S, Gotzche P, Vandenbroucke J. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12:1495–9.
9. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated 2017. Available from http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/.
10. ATS/ERS Task Force: Standardisation of lung function testing. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
11. ATS/ERS Task Force: Standardisation of lung function testing. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
12. Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Culver B, et al. Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. Eur Respir J. 2012;40(6):1324–43, http://dx.doi.org/10.1183/09031936.00080312.
13. Kim M, Rhee C, Kim K, Kim S, Lee J, Kim Y, et al. Heterogeneity of asthma and COPD overlap. Int J COPD. 2018;13:1251–60.
14. Delgado A, Lima M. Contribution to concurrent validity of treatment adherence [Contributo para a validação concorrente de uma medida de adesão aos tratamentos]. Psicologia, Saúde e Doenças. 2001;2(2):81–100.
15. Sanchis J, Corrigan C, Levy M, Viejo J. Inhaler devices – from theory to practice. Respir Med. 2013;107:495–502.
16. Molen T, Pieters W, Bellamy D, Taylor R. Measuring the success of treatment for chronic obstructive pulmonary disease – patient, physician and healthcare payer perspectives. Respir Med. 2002;96(C):s17–21.
17. Makela M, Backer V, Hedegaard M. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. Respir Med. 2013;107(10):1481–90.
18. George J, Kong D, Thoman R, Stewart K. Factors associated with medication nonadherence in patients with COPD. Chest. 2005;128:3198–204.
19. Rootmensen G, Keimpema A, Jansen H, Haan R. Predictors of incorrect inhalation technique in patients with asthma and COPD: a study using a validated videotaped scoring method. J Aerosol Med Pulm Drug Deliv. 2010;23(5):1–6, http://dx.doi.org/10.1089/jamp.2009.0785.
20. Maricoto T, Rodrigues L, Teixeira G, Valente C, Andrade L, Saraiva A. Assessment of inhalation technique in clinical and functional control of asthma and chronic obstructive pulmonary disease. Acta Med Port. 2015;28(6):702–7.
21. Usmani O, Lavorini F, Marshall J, Dunlop C, Heron L, Farrington E, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res. 2018;19:10, http://dx.doi.org/10.1186/s12931-017-0710-y.
22. Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A, et al. Chronic obstructive pulmonary disease exacerbations inhaler handling: real-life assessment of 2935 patients. Eur Respir J. 2017;49:1601794.
23. Melani A, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011;105:930–8.
24. Liang C, Chen Y, Sheu S, Tsai C, Chen W. Misuse of inhalers among COPD patients in a community hospital in Taiwan. Int J COPD. 2018;13:1309–16.
25. Chan K, Ko F, Chan H, Wong M, Mok T, Choo K, et al. Adherence to a COPD treatment guideline among patients in Hong Kong. Int J COPD. 2017;12:3371–9.
26. Miravitlles M, Murio C, Tirado-Conde G, Levy G, Muellerova H, Soriano J, et al. Geographic differences in clinical characteristics and management of COPD: the EPOCA study. Int J COPD. 2008;3(4):803–14.
27. Turan O, Emre J, Deniz S, Baysak A, Turan P, Mirici A. Adherence to current COPD guidelines in Turkey. Expert Opin Pharmacother. 2016;17(2):153–8.
28. Asche C, Leader S, Plauschinat C, Raparla S, Yan M, Ye X, et al. Adherence to current guidelines for chronic obstructive pulmonary disease (COPD) among patients treated with combination of long-acting bronchodilators or inhaled corticosteroids. Int J COPD. 2012;7:201–9.
29. Gross N. Chronic obstructive pulmonary disease outcome measurements. What's important? What's useful? Proc Am Thorac Soc. 2005;2:267–71.
30. Jones P. Progress in characterizing patient-centred outcomes in COPD, 2004–2014. J COPD Found. 2014;1(1):17–22.
31. Harper R, Brazier J, Waterhouse J, Walters S, Jones N, Howard P. Comparison of outcomes measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. Thorax. 1997;52:879–87.
32. Plaza V, López-Vina A, Cosio B. In representation of the Comité Científico del proyeto TAI. Test of adherence to inhalers. Arch Bronconeumol. 2017;53(7):360–1.

Pulmonol. 2020;**26(2)**:73–77

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

The Portuguese version of Rhinitis and Asthma Patient's Perspective (RAPP): Validation and assessment

A. Todo-Bom[a], F. Braido[b], G. Molinengo[c,*], C. Loureiro[d], G.W. Canonica[e,f], I. Baiardini[f]

[a] *Faculty of Medicina, University of Coimbra and Immunoallergology Department, Coimbra University Hospital, Portugal*
[b] *Department of Internal Medicine, Respiratory Diseases and Allergy Clinic, University of Genova – Azienda Policlinico IRCCs San Martino, Genova, Italy*
[c] *Department of Psychology, University of Turin, Turin, Italy*
[d] *Immunoallergology Department, Coimbra University Hospital, Portugal*
[e] *Personalized Medicine, Asthma and Allergy Clinic, Humanitas Research Hospital, Milan, Italy*
[f] *Department of Biomedical Sciences, Humanitas University, Milan, Italy*

Received 6 July 2018; accepted 12 October 2018
Available online 5 February 2019

KEYWORDS
Allergic rhinitis;
Asthma;
Clinical practice;
Cross-cultural validation;
Health Related Quality of Life

Abstract
Background: Allergic rhinitis (AR) and asthma are two common chronic diseases that often coexist. There is a need for a validated tool to evaluate HRQoL of Portuguese speakers with asthma and/or rhinitis patients in clinical practice.
Objectives: To adapt and validate RhinAsthma Patient Perspective (RAPP) in Portuguese.
Methods: The RAPP questionnaire was translated into Portuguese. Asthmatics with comorbidities and rhinitis attending the allergy department of Coimbra University Hospital were asked to complete the Portuguese translation of RAPP, in addition to the SF-12, ACT, and a Symptomatologic VAS twice, with a 4-week interval between visits. During Visit 2, a Global Rating Scale (GRS) was completed to assess any change in health status. Scale dimensions, internal consistency and convergent validity, reliability, discriminant ability and responsiveness to change, as well as Minimal Clinical Difference were assessed.
Results: Factor and confirmatory analysis confirm the unidimensional structure of the questionnaire. Internal consistency has been shown to be satisfactory (0.82 visit 1 and 0.86 at visit 2). The tool is able to discriminate between patients on the basis of asthma severity, asthma control level, and rhinitis severity; convergent validity showed a significant correlation with SF-2 Physical component ($r = -0.46$ and 0.42, p at Visits 1 and 2). An ICC of 0.97 and a CCC = 0.94 indicate that the tool is highly reliable. Responsiveness was shown in detecting a significant association with GRS changes ($r = 0.41$, $p < 0.01$) and ACT ($r = -0.47$, $p < 0.01$) but not with VAS. ($r = .14$, *n.s.*). MID value was 2 points.

* Corresponding author.
E-mail address: giorgia.molinengo@unito.it (G. Molinengo).

https://doi.org/10.1016/j.pulmoe.2018.10.009

Conclusions: The Portuguese version of RAPP has been demonstrated to have good measurement properties and sensitivity to health changes, which will provide a valid, reliable and standardized HRQoL measurement in patients with asthma and comorbid allergic rhinitis in clinical practice.

Introduction

Allergic rhinitis (AR) and asthma are two common chronic diseases that often coexist: up to 80% of patients with asthma suffer from AR, while 10–40% of patients with AR also have asthma.[1–4] These diseases represent a significant socio-economic burden on both individuals and society as a whole due to the high direct and indirect costs.[5] Moreover, there is now considerable evidence that AR and asthma significantly impair Health Related Quality of Life (HRQoL). In fact, the availability of validated questionnaires has assisted the measurement of the impact of respiratory allergies from a patient perspective and has produced a rich literature on the ways that asthma and AR negatively affect patient physical, emotional, mental and social life.[5,6] However, if HRQoL has become increasingly considered as an outcome measure in clinical trials, its integration into routine assessment remains challenging. This depends primarily on the lack of questionnaires that are specifically validated for use with individual patients.

RhinAsthma Patient Perspective (RAPP) is a validated tool of 8 questions, available in Italian,[7,8] that provides evaluation of HRQoL of patients with asthma and/or rhinitis in clinical practice. Patients are asked to grade the extent to which they have been bothered by each problem during the previous 2 weeks using a 5-point Likert-type scale (not at all, a little, quite, a lot, and very much). The tool is simple to complete and the score is a simple sum of the single answers (range 8–40). A cutoff point of 15 demonstrated the best sensitivity and specificity in discriminating the achievement of an optimal HRQoL. The RAPP owns the psychometric properties that are requested for the use of an instrument with an individual patient.[9,10]

The aim of this study was to cross-culturally adapt and validate the RAPP in Portuguese. This project was part of a larger multinational study aimed at evaluating the psychometric properties of the RAPP in five countries (Spain, France, Portugal, Poland and the Philippines) and to compare HRQoL in the countries involved.

Materials and methods

The process of cross-cultural adaptation was conducted according to international guidelines with 2 forward and backward translations.[11] Once the Portuguese version was obtained, patients who visited the Immunoallergology Department, Coimbra University Hospital, Portugal, were prospectively enrolled between June and December 2017. Data was collected using a convenience sampling method.[12] The aim was to include 150 patients. The inclusion criteria were: age $\geq$18, asthma and/or rhinitis diagnosis according to GINA and ARIA guideline and willingness to be enrolled into the study. Patients suffering from any other respiratory or ear–nose–throat disorders were excluded.

The study was approved by the ethics committee of the University of Genoa (approval no. P.R. 333REG2016) and ratified by the local ethics committee; it was conducted in accordance with the general principles of Good Clinical Practice and the Declaration of Helsinki as amended in Edinburgh in 2000. Each patient gave written informed consent to participate at the beginning of the study.

Patients were assessed twice, with a 4-week interval between visits. At the first visit, a physician collected a complete and accurate medical history and recorded ongoing therapy. Their last available spirometric value was registered. Smoking status was collected and patients were classified as current smokers, former smokers or non-smokers. At each visit patients filled in the RAPP questionnaire, SF-12 to assess health status, asthma control test (ACT), and a Symptomatologic Visual Analog Scale (VAS) to evaluate rhinitis severity. At Visit 2, a Global Rating Scale was completed to evaluate any change in health status.

In order to validate the Portuguese version of RAPP, the following psychometric analyses were performed:

1) Scale's dimension by mean of explorative and confirmative factor analysis.[13,14] In more detail, the Kaiser–Meyer–Olkin (KMO) test was adopted to analyze the feasibility of factor analysis, and Bartlett's Test of Sphericity was chosen to test for null hypothesis that the correlation matrix has an identity matrix. The root-mean-square error of approximation (RMSEA), comparative fit index (CFI), and standardized root mean squared residual (SRMR) were used to assess fit.
2) Internal consistency was measured using Cronbach's alpha on the whole test. Values >0.70 are generally considered acceptable,[15] whereas higher scores are recommended for use in an individual patient.[16]
3) Reliability was assessed in patients with a stable health status (GRS = 0) by means of interclass coefficient (ICC) and Lin's concordance correlation coefficient (CCC).[17] Coefficients of 0.70 for group comparisons and of 0.90 for comparisons within individuals are recommended.[13]
4) Convergent validity was evaluated using Spearman's between RAPP and SF-12. Correlations ranged from 0.4 to 0.8 confirm the convergent validity.

5) Discriminant validity was assessed by means of ANOVA (Fischer's test) comparing patients according to ACT, GINA and ARIA classification of severity.
6) Responsiveness was evaluated by analyzing the correlation between changes in RAPP scores and changes in GRS, VAS and ACT by means of a non-parametric test (Spearman correlation coefficient).
7) Minimal important difference (MID) was determined by applying the receiver operating characteristics (ROC) curve method. The entire cohort for one dichotomization point (i.e., 'no change' vs 'any improvement or deterioration') was adopted.[18]

The possible effect of age, education, and smoking habits on patients' answers was explored by means of Spearman's correlation coefficient and ANOVA Fischer's test.

The frequency distribution of answers was calculated to verify whether patients were using the entire answer scale.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics, version 24, Armonk, NY while confirmatory factor analysis was performed using Mplus 7.0 (Muthén & Muthén, Los Angeles, CA).[19]

Results

The validation sample consisted of 149 patients (65% females). The mean age was 36.8 (age range 18–81 years). Of the respondents, 4.2% were current smokers, 10.3% former smokers and 85.5% non-smokers. Academic degree was the most common level of education attained (55.3%), followed by high school (36.6%), secondary school (6.5%) and primary school (1.6%) qualifications. 61.1% of patients suffered from persistent asthma and 38.9% from intermittent asthma. AR was classified as mild intermittent in 24.2% of all cases, moderate–severe intermittent in 3.6%, mild persistent in 14.8%, and moderate–severe persistent in 56.4% according to ARIA guidelines.[1] The ACT score at Visit 1 showed 31.7% to be totally controlled, 49.7% to be well controlled, and 18.6% to be uncontrolled. The effective time between the two visits was 28 ± 3 days.

The mean value of AR and asthma quality of life was 16.9 ± 5.5 at visit 1 and 16.8 ± 5.6 at visit 2.

1) Scale dimensions confirmed that the data were suitable for factor analysis. The solution revealed a unidimensional structure that absorbed 37.8% of the total variance and only 4 residuals greater than |0.10| at visit 1 and 43.4% of the total variance and only 2 residuals greater than |0.10| at visit 2. The unidimensional structure was confirmed: the goodness-of-fit indexes were all satisfactory both at visit 1 (RMSEA 0.08, SRMR 0.05, CFI 0.91) and at visit 2 (RMSEA 0.09, SRMR 0.06, CFI 0.90)
2) Internal consistency: Cronbach alpha values were 0.82 at visit 1 and 0.86 at visit 2, both satisfactory.
3) Reliability was evaluated in 43 patients reporting an unchanged health status (GRS = 0) showing an ICC of 0.97 and a CCC = 0.94.

Table 1 (RAPP) discriminant validity.

	Rapp score	
	Visit 1	Visit 2
Asthma		
Mild	16.8	16.5
Moderate	14.4	14.2
Severe	18.3	18.5
p-value	*0.035*	*0.016*
ACT		
Totally controlled	14	13.1
Well controlled	17.1	16.4
Uncontrolled	21.4	23
p-value	*<0.01*	*<0.01*
Rhinitis		
Intermittent	14.8	14.3
Persistent	17.8	17.7
p-value	*0.003*	*0.001*
Rhinitis severity		
Mild	14.5	14.1
Moderate–severe	18.5	18.5
p-value	*<0.01*	*<0.01*

4) Convergent validity: correlations between RAPP scores and the Physical Component Score of SF-12 were significant both at Visit 1 ($r = -0.42$, $p < 0.01$) and at Visit 2 ($r = -0.46$, $p < 0.01$), while correlations were not significant between RAPP and the Mental Component Score of SF-12 either at Visit 1 ($r = -0.05$, *n.s.*) or Visit 2 ($r = -0.02$, *n.s.*).
5) Discriminant validity: RAPP was able to discriminate between patients on the basis of asthma severity, asthma control level, and rhinitis severity (Table 1).
6) Responsiveness was assessed in 106 patients with a health improvement or deterioration, evaluated by GRS $\neq 0$. RAPP was significantly associated with changes in GRS ($r = 0.41$, $p < 0.01$) and ACT ($r = -0.47$, $p < 0.01$) while the association with VAS was not significant ($r = .14$, *n.s.*).
7) MID: A 2 point difference or change in RAPP maximizes sensitivity, specificity, and the number of individuals correctly classified (Table 2).

No significant difference was reported in RAPP scores between smokers, former smokers, and nonsmokers (ANOVA Fisher's test. Visit 1: $p = 0.06$; Visit 2: $p = 0.11$) nor on the basis of level of education (ANOVA Fisher's test. Visit1:

Table 2 The MID of RAPP obtained with the ROC analysis with different cutoff.

Cutoff ≥	Sensitivity	Specificity
5	.977	.451
4	.977	.539
3	.953	.686
2[a]	.912	.833
1	.884	.931

[a] Cutoff point chosen.

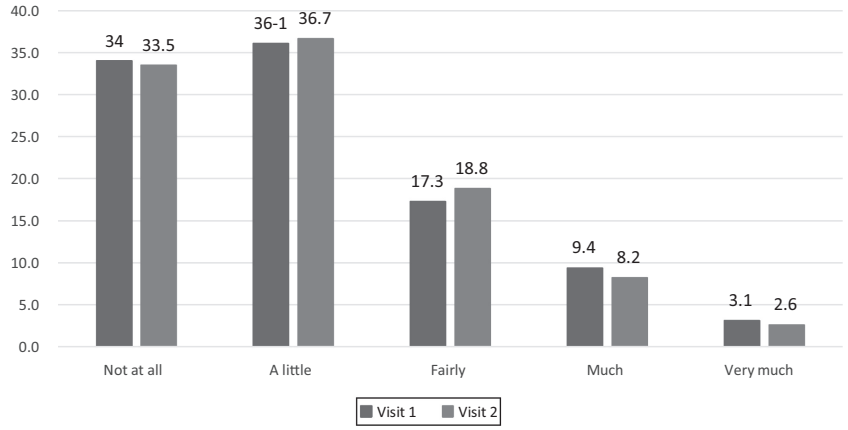

Figure 1 Frequency distribution of RAPP answers at Visit 1 and at Visit 2.

$p = 0.679$; Visit 2: $p = 0.476$). Significant associations were found between age and RAPP scores (Spearman's correlation. Visit 1: $r = 0.23$, $p = 0.005$; Visit 2, $r = 0.31$, $p < 0.01$).

The frequency distribution of answers at Visit 1 and at Visit 2 shows that the entire scale range had been used (Fig. 1).

Discussion

In daily clinical practice, therapeutic management of patients with comorbid asthma and allergic rhinitis is primarily decided by the physician according to the patient's symptoms and biological parameters. Little emphasis is given to the patients' perspective of the impact of their disease and its treatment upon their quality of life. This is mainly due to the lack of simple and reliable tools for assessing HRQoL in daily routine; the questionnaires available are too long and complex for routine clinical use.[20]

RAPP has been validated in Italian according to the available guidance to properly assess the patient's perspective in clinical practice[21,22] and a cross-cultural validation is needed to use this tool in everyday practice in other languages. To perform this process we selected specific tools that are widely used for the validation process of HRQoL questionnaires and which are available in the languages needed for all countries involved in this international study. For this reason, it was not possible to assess the level of control both in asthma and AR. In fact, although tools specifically designed to assess control are available for asthma (ACT), rhinitis (ARCT)[23] and concomitant asthma and rhinitis (e.g. CARAT),[24] only for the ACT do we have a validated version in Spain, France, Portugal, Poland and the Philippines. For this reason, we decided to include the ACT in our protocol and to evaluate symptom severity instead of control in AR, by mean of VAS. This prospective study was performed to validate the Portuguese version.

We found the Portuguese version of the RAPP to be reliable for the individual assessment of HRQL. Our analyses confirmed the unidimensional structure of the tool and the results of factorial analysis explain more than 40% of variance, proving its strong validity.

In terms of reliability, the Portuguese version of the RAPP performed well in the present validation study, with Cronbach-α values over the recommended 0.70 threshold for the overall score. Internal consistency results were generally comparable with, or better than, those seen for the original instrument. Satisfactory convergent and discriminant validity and high responsiveness to changes were confirmed. The lack of effect of demographic characteristics on patients' answers makes the questionnaire appropriate for use in everyday practice.

Since asthma and rhinitis symptoms can vary over time, the availability of a patient-reported outcomes measure which is capable of mirroring these changes is significant. As in the original version, a 2 point change in RAPP score identified a HRQL change perceived by the patient.

The present study has several strengths. First of all it confirms the psychometric properties of RAPP in a language different from the original one. Moreover it offers the possibility of assessing HRQoL in the routine clinical management of Portuguese patients with asthma and AR and to compare the HRQoL of the Portuguese-speaking population with other patients from different countries.

One limitation of our study is the generalizability of the results: patient selection bias cannot be excluded since the patients were recruited from one single specialist center and the sample was nonrandomized. Moreover, the acceptability of the RAPP for both patients and physicians and the added value of using this tool in clinical practice have not been assessed. These limitations may be addressed through further studies including other settings and by assessing acceptability and clinical relevance.

In conclusion, this study demonstrates that the Portuguese RAPP version is suitable for use among asthma and allergic rhinitis patients both in research and clinical settings.

Funding

This work was supported by Menarini International Operations Luxemburg S.A. (M.I.O.L.). Contract ARMIA_M.I.O.L. 19/09/2016.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

The authors thank ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche) for scientific support.

References

1. Bousquet J, Khaltaev N, Cruz AA, J., W.J., A., et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl. 86:8–160.
2. Cingi C, Gevaert P, Mosges R, C., V., M., et al. Multi-morbidities of allergic rhinitis in adults: European Academy of Allergy and Clinical Immunology Task Force Report. Clin Transl Allergy. 2017;7:17–23.
3. Cruz AA, Popov T, Pawankar R, Annesi-Maesano I, Fokkens W, Kemp J, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in with GA(2)LEN. Allergy. 2007;62 Suppl. 84:1–41.
4. Ozdoganoglu T, Songu M. The burden of allergic rhinitis and asthma. Ther Adv Respir Dis. 2012;6:11–23.
5. Linneberg A, Dam Petersen K, Hahn-Pedersen J, Hammerby E, Serup-Hansen N, Boxall N. Burden of allergic respiratory disease: a systematic review. Clin Mol Allergy. 2016;14:12.
6. Meltzer EO. Allergic rhinitis: burden of illness, quality of life, comorbidities, and control. Immunol Allergy Clin North Am. 2016;36:235–48.
7. Braido F, Baiardini I, Stagi E, Scichilone N, Rossi O, Lombardi C, et al. Rhinasthma patient perspective: a short daily asthma and rhinitis QoL assessment. Allergy. 2012;67:1443–50.
8. Molinengo G, Baiardini I, Braido F, Loera B. RhinAsthma patient perspective: a Rasch validation study. J Asthma. 2017;4:1–5.
9. National Quality Forum. Patient reported outcomes (PROs) in performance measurement [Internet]. Washington, DC: NQF; 2013. Available from: https://www.qualityforum.org/Publications/2012/12/Patient [accessed 02.05.18]. International Society for Quality of Life Research.
10. User's guide to implementing patient-reported outcomes assessment in clinical practice. Available from: http://www.isoqol.org/UserFiles/2015UsersGuide-Version2.pdf. Version: January 2015 [accessed 02.05.18].
11. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Health. 2005;8:94–104.
12. MacCallum RC, Browne MW, Sugawara HM. Power analysis and determination of sample size for covariance structure modeling. Psychol Methods. 1996;1:130–49.
13. Streiner DL. Health a practical guide to their development and use. 3rd ed. Oxford: Oxford University Press; 2003.
14. Brown MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, editors. Testing structural equation models. Newbury Park, Calif: Sage; 1993. p. 136–62.
15. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16:297–334.
16. Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res. 2002;11:193–205.
17. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics. 1989;45:255–68.
18. Turner D, Schunemann HJ, Grif fi th LE, Beaton DE, Grif fi ths AM, Critch JN, et al. Using the entire cohort in the receiver operating characteristic analysis maximizes precision of the minimal important difference. J Clin Epidemiol. 2009;62:374–9.
19. IBM Corporation. IBM SPSS Missing Values 20. Available from: https://www.csun.edu/sites/default/files/missing-values20-64bit.pdf [accessed 02.04.18].
20. Baiardini I, Braido F, Molinengo G, Caminati M, Costantino M, Cristaudo A, et al. Chronic urticaria patient perspective (CUPP): the first validated tool for assessing quality of life in clinical practice. J Allergy Clin Immunol Pract. 2018;6:208–18.
21. National Quality Forum. Patient reported outcomes (PROs) in performance measurement [Internet]. Washington, DC: NQF; 2013. Available from: https://www.qualityforum.org/Publications/2012/12/Patient [accessed 02.05.18].
22. International Society for Quality of Life Research. User's guide to implementing patient-reported outcomes assessment in clinical practice. Available from: http://www.isoqol.org/UserFiles/2015UsersGuide-Version2.pdf. Version: January 2015 [accessed 02.05.18].
23. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. Clin Exp Allergy. 2011;41:860–8.
24. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy. 2010;65:1042–8.

Pulmonol. 2020;**26(2)**:78–83

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Preventive therapy compliance in pediatric tuberculosis – A single center experience

J.C. Santos[a,*], J.B. Silva[a], M.A. Rangel[a], L. Barbosa[a,b], I. Carvalho[a,b,c]

[a] *Pediatrics Department, Vila Nova de Gaia/Espinho Hospital Center, Rua Dr. Francisco Sá Carneiro, 4400-129 Vila Nova de Gaia, Portugal*
[b] *Pediatric Tuberculosis, Pneumologic Diagnosis Center, Rua do Conselheiro Veloso da Cruz 383, 4400-088 Vila Nova de Gaia, Portugal*
[c] *Allergy and Pulmonology Pediatrics Unit of Pediatrics Department, Vila Nova de Gaia/Espinho Hospital Center, Rua Dr. Francisco Sá Carneiro, 4400-129 Vila Nova de Gaia, Portugal*

Received 12 April 2019; accepted 10 June 2019
Available online 17 August 2019

KEYWORDS
Tuberculosis;
Chemoprophylaxis;
Children;
Compliance;
Latent tuberculosis infection;
Isoniazid

Abstract
Introduction: Despite its importance, there are some barriers to patient compliance in preventive therapy (PT) of tuberculosis (TB). The purpose of this study was to evaluate the compliance to appointments, PT and follow-up in a pediatric population after TB exposure, followed in a single TB outpatient center, and the subsequent identification of compliance determinants.
Methods: Retrospective analysis of all pediatric patients who underwent PT in Gaia TB outpatient center from January 2015 to June 2016. Patients were divided into two groups: compliant and non-compliant, according to adherence to screening, visits and medication. The data collection was based on review of medical records.
Results: A total of 72 patients were enrolled, 33 (45.8%) on chemoprophylaxis and 39 (54.2%) on latent tuberculosis infection (LTBI) treatment. The majority of patients were compliant (63.9%, $n = 46$). Non-compliance was found in 36.1% ($n = 26$): in 12 patients to contact screening, in 11 patients to PT and 22 patients did not attend medical appointments in the first place. In 10 patients, non-compliance was related to social problems/family dysfunction (low socioeconomic status and parent's unemployment). After putting in place several strategies, such as telephone contact, activating social services and direct observation of therapy, a compliance of 98.6% was achieved. Isoniazid was the main drug used (91.7%), during 9 months for LBTI.

* Corresponding author.
E-mail address: joana.alves.santos@chvng.min-saude.pt (J.C. Santos).

https://doi.org/10.1016/j.pulmoe.2019.06.002

Conclusion: PT compliance in TB can be challenging, probably related to the lack of risk perception and caregiver's reluctance to undergo a prolonged treatment to an asymptomatic condition. We conclude that implementing interventions can considerably improve treatment compliance and reduce the risk of future tuberculosis development. We emphasize the success in compliance to a 9 month regimen of isoniazid in the vast majority of patients with LTBI.

Introduction

Tuberculosis (TB) remains an important infectious disease in pediatric age group.[1–3] Although a low incidence threshold for tuberculosis was achieved in 2015 in Portugal (incidence of tuberculosis < 20/100,000 habitants),[4] children remain at higher risk for developing tuberculosis.

After *Mycobacterium tuberculosis* (*Mt*) infection, children, especially those under 6 years old, have a higher probability of developing the disease, usually in the first two years following infection.[1,5] TB contact screening and implementation of preventive therapy (PT) remain as important measures to reduce the risk of progression to TB.[5] TB contact screening is carried out in TB outpatient centers after TB exposure and in candidates to immunosuppressive therapies.[6]

PT is indicated when latent tuberculosis infection (LTBI) is diagnosed and as chemoprophylaxis (CP) in children under 6 years old after TB exposure.

LTBI diagnose is based on a positive immunological test, and PT is continued with isoniazid for 6–9 months. Alternative regimens, such as 4 months rifampicin, may be an option in cases of resistance to isoniazid, or adverse events. Efficacy is described in the literature as 90% with 9-months of isoniazid, 69% with 6-months of isoniazid and 59% with 3–4 months of rifampicin.[6,7] Most recently, another regimen has emerged, with twelve doses of weekly rifapentine plus and isoniazid for 3 months. This last regimen has shown to be equivalent to isoniazid in children aged 2 years and older, but with higher compliance.[6,8]

There has been some controversy about the best PT,[9,10] with some authors defending shorter anti-TB drugs regimens in order to improve compliance.[8,11] Compliance to a long-term daily treatment is crucial to TB control. The primary objective of this study was to determine the compliance rate to TB PT in a cohort of children and adolescents receiving TB drugs as primary chemoprophylaxis, or as LTBI treatment, identifying failure compliance determinants. The evaluation of implementation of strategies to improve PT compliance was a secondary objective of this study.

Methods

We carried out a retrospective cohort study, based on medical records review, on the compliance to PT (CP or LTBI treatment) and to scheduled appointments in pediatric patients (<18 years of age) followed-up from January 2015 to June 2016 at Gaia outpatient TB center, a TB reference center at the north region of Portugal. This center is a community referral center for tuberculosis in the city of Gaia, Portugal, where all children/adolescents of this region who have been exposed to someone with tuberculosis or with suspected tuberculosis disease are screened, investigated and treated, including patients with *Mt* sensitive to antitubercular drugs and multidrug-resistant cases. Chemoprophylaxis was prescribed after TB contact with a smear-positive patient for children younger than 6 years, after exclusion of active tuberculosis and discontinued 8–12 weeks later, after a second negative screening. The drug of choice was isoniazid, unless index case was resistant to isoniazid, in which case rifampicin was chosen. LTBI diagnosis was made in case of positive IGRA/TST in children younger than 6 years of age or both positive TST and IGRA in children $\geq$6 years old, asymptomatic and with normal chest X-ray. LTBI treatment consisted of a 9-month regimen of isoniazid monotherapy or, in case of resistance to isoniazid of index case or intolerance/side effects to isoniazid, 4-months regimen of rifampicin. Medication was given to parents/caregivers once a week, free of charge, daily dosing was indicated and administered by parents at home. All patients on PT were seen monthly until the treatment was complete both to improve compliance and to check for symptoms or adverse effects. Demographic characteristics, clinical findings at admission, side effects to the regimens, workup and strategies to improve compliance, were collected from patient medical record. Patients were divided into two groups: (a) compliant – those patients who attended all the scheduled appointments/screening procedures and completed the proposed PT; (b) non-compliant – considered to be failure on medication regimen or presence of other factors that raised the suspicion of non-compliance (missing to one or more medical appointment or screening). Reasons for non-compliance were classified from the perspective of the patient's medical doctor through review of clinical records. Social problems/family dysfunction were defined by the presence of any of the following criteria: (1) families in which conflict and child neglect occurred and was noticed during medical appointments; (2) families shown to be at risk by the protection commission for children and adolescents; (3) alcohol or drug abuse of any of the parents; (4) low socioeconomic status and parental unemployment. All data analyses were performed using the SPSS, version 24.0. Statistical significance was determined at the level of $p < 0.05$. Confidence intervals were set at 95%. Categorical variables are described as frequencies and percentages,

and continuous variables as means and standard deviation or medians and interquartile ranges, respectively. Differences between compliant and non-compliant were tested using χ^2 test or Fisher exact test for categorical variables and Student's *t*-test or Mann–Whitney test for independent samples, as appropriate.

Results

A total of 72 patients were enrolled, 33 (45.8%) on CP and 39 (54.2%) on LTBI. The overall results are synthesized in Fig. 1.

Sociodemographic data are described in Table 1. The median age was 5.5 years, and it was significantly lower in the CP group comparing with LTBI group (2.9 vs. 7.7 years, respectively; $p < 0.001$). Globally there was a male predominance. Patients were referred to our center mostly by public health services, especially after exposure to tuberculosis ($n = 63$). The index case was intrafamilial in the majority of patients (79.2%), with a predominance of grandparents ($n = 20$); with a daily contact ($n = 35$). *Mt* of the index case was susceptible to all drugs in 90% of cases. There were 4 patients referred to screening for immune mediated inflammatory diseases candidates for biologic therapy or other immunosuppressive agents. Patients were vaccinated with BCG-vaccine (100%, $n = 68$; 4 missing values), according to the universal BCG vaccination standard in practice at that time. At the time of the first medical consultation, 17 patients (23.6%) had symptoms (cough and/or fever). Isonazid was started in 67 patients (93.1%) and rifampicin in 5 patients (6.9%, for isoniazid-resistant *Mt* of the index case). In case of CP, treatment was continued for a mean of 9.7 ± 3.1 weeks and till a second screening ruled out LTBI. The second screening was preformed 9.7 weeks after the first one and included TST and IGRA. Complete blood count and liver function tests were performed in 33.4% of patients ($n = 24$) after the initiation of treatment, with normal results.

There was compliance to screening, visits and treatment in 63.9% ($n = 46$) and non-compliance in 36.1% ($n = 26$; Fig 1). A stratified analysis of the results according to the type of treatment (CP vs. LTBI) revealed a compliance of 75.8% ($n = 25$) in CP group and 53.8% ($n = 21$) in LTBI, $p = 0.054$. Patient age was significantly higher in non-compliant group (6.9 ± 4.7 years-old vs. to 4.8 ± 3.8 in compliance group, $p = 0.046$). Social problems/family dysfunction were present in 38.5% ($n = 10$) patients, all non-compliant ones.

Missing appointments were registered in 30.6% ($n = 22$) and were related with age $\geq$6 years old (46.2% vs. 21.9% in children <6 years old; $p = 0.031$). Of those who missed appointments, 36.4% ($n = 8$) failed to complete the treatment. There was an association between missing appointments and failure in treatment ($p = 0.002$). A group of 14 patients maintained treatment despite missing medical appointments (19.4%) and this group was significantly older (mean age 8.9 ± 4.0 vs. 4.8 ± 3.8 years old; $p = 0.003$) and mostly on LTBI treatment ($n = 12$; 85.7%). Patients in CP had a median of 4 (IQR 3–6) medical appointments and LTBI patients a median of 7 (IQR 4:8).

The reasons found for non-compliance are described in Fig. 2, and included social problems/family dysfunction and medication problems, which consisted of symptoms related with medication such as nausea, vomiting or other gastrointestinal symptoms, side effects and intolerance to treatment. Non-compliance to contact screening was found in 12 patients and in 11 patients (15.3%) to PT. In 10 patients, non-compliance was related to family dysfunction/social problems. Medication side effects were seen in 3 patients (4.2%), with one patient needing to change isoniazid to rifampicin (9.1%), with subsequent compliance to treatment. Oral intolerance to medication was seen in 1 patient (9.1%). For 2 patients there was no explanation found to non-compliance to treatment. Follow-up of patients was monthly until treatment was complete.

When non-compliance of any kind was noticed, some strategies were implemented (Fig 2): all parents/caregivers were contacted by phone and encouraged to return to the appointments and take the medication, rescheduling a new appointment ($n = 26$; 100%); social service was activated in order to help the return of these families to the appointments ($n = 2$; 7.7%); directly observed treatment was implemented ($n = 1$; 3.8%); change in medication (3.8%) and shortening of the time of prescription ensuring regular and closer monitoring of drug supply (7.7%). With the implementation of these strategies, a final compliance rate of 98.6% was achieved ($n = 71$). There was 1 case of loss of follow-up. Isoniazid was the main drug used ($n = 66$; 91.7%), in 31 cases of CP with a median duration of 9 (IQR 8:12) weeks and in 35 cases of LTBI for 9 months, with a compliance of 97.1% to 9-month regimen with isoniazid. Rifampicin was used for four months in 8.3% ($n = 6$), one for side effects to isoniazid and 5 for resistance to isoniazid in the index case. There was no statistical significant difference in PT compliance between rifampicin and isoniazid (83.3% vs 62.7%; $p = 0.658$).

Discussion

Tuberculosis in childhood represents a missed opportunity for TB screening and establishment of PT.[12] PT has the aim of precluding occurrence of disease in those already infected or exposed to TB. Despite its importance, there are some barriers, usually related with long PT courses and the lack of perception of the risk of TB development by the parents/caregivers in the asymptomatic child.[2] The compliance to prolonged regimens is another difficult issue. In our study, initial compliance to PT was 63.9%, which was slightly inferior to another study that reported 72.8% of compliance to CP ant LTBI treatment in pediatric age.[13] There was no statistical significant differences in the PT compliance between CP and LTBI patients (75.8% vs 53.8%, $p = 0.054$), as also reported by Guix-Comellas et al.,[13] which described an adherence of 24.3% by CP patients and 35.1% by LTBI patients, $p = 0.08$, although with shorter regimens, young children on CP usually depend on their parents and are likely to adhere better to medical therapies. Older age was associated with non-compliance ($p = 0.046$), consistent with another study that reported adolescence as a risk factor for non-compliance.[13] Another study about treatment completion for LTBI reported 65.7% of treatment compliance, with significant higher adherence with 4-month rifampicin (85%) compared to isoniazid (52%).[8] However, in our study no significant differences were found in the compliance between isoniazid and rifampicin (83.3% vs 62.7%; $p = 0.658$), although

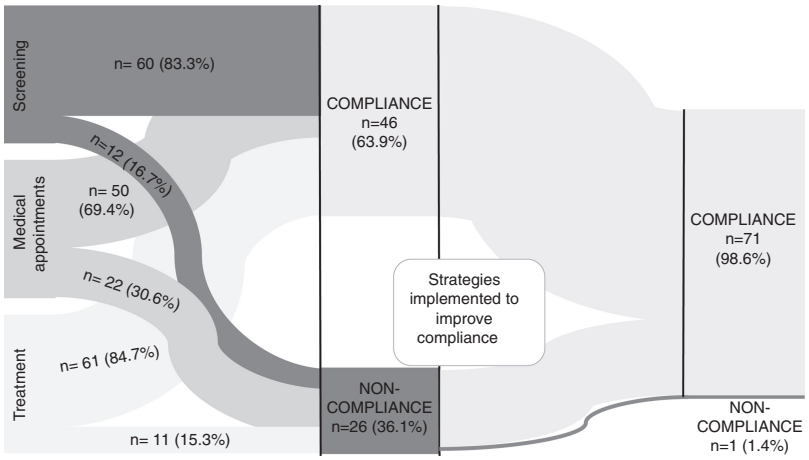

Figure 1 Results overview.

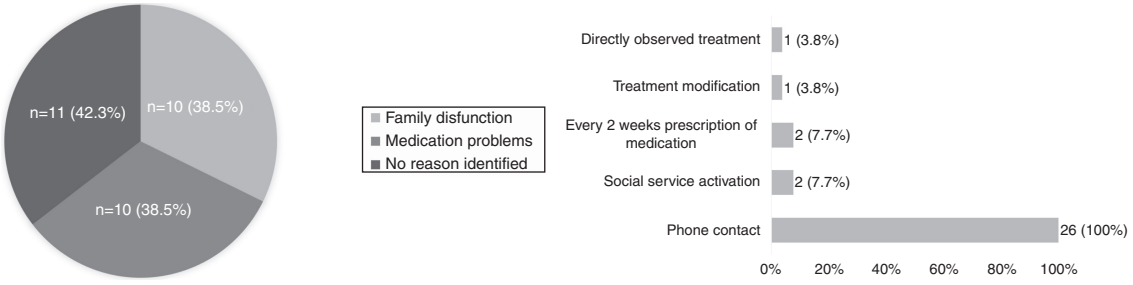

Figure 2 Reasons to non-compliance and strategies implemented to improve compliance.

the small number of patients on rifampicin may have limited the conclusions. In our population, isoniazid for 9 months was the chosen regimen, with 90% efficacy described in the literature.[6,7,14] In cases in which *Mt* strains of the index case were resistant to isoniazid or intolerance to isoniazid was observed, a 4-month regimen with rifampicin was used, as described in the literature.[6] Some studies suggest other shorter regimens with higher completion rates, such as 6-month therapy with isoniazid, with an efficacy of 69%,[5] 3–4 month of daily isoniazid plus rifampicin[6] or twelve doses once-weekly with isoniazid and rifapentine, although this last regimen is not recommended for children younger than 2 years of age but has an estimated efficacy of 90%, equivalent to 9-months of isoniazid.[6]

The main barriers to PT implementation identified in different studies[16,17] are, lack of awareness, lack of risk perception among parents, inadequate knowledge among healthcare providers and poor programmatic monitoring. However, in our study, social problems/family dysfunction and medication problems were the main reasons identified for non-compliance. We believe that our community-based approach with collaboration of pediatricians with experience in tuberculosis, with closer contact with families and regular scheduled appointments was responsible for an increased awareness of the health care providers to TB PT importance, reducing this non-compliance determinant reported in other studies. Another study in Ethiopia[17] about compliance to isonazid CP reported poor compliance (12%) with the main reason being the perception that drugs were not necessary when the child was healthy.

Drug-related adverse effects were low, with just one patient needing to change medication. Routine liver function monitoring is not necessary for children unless they have liver disease[10] and in our population they were performed in 33.4% of cases once during the treatment course. Household contacts were the most frequent source of infection, as also described by others.[8,13]

The implementation of several strategies was successful in the compliance improvement, achieving a final compliance of 98.6%. To the best of our knowledge, this is the first study in Portugal about PT compliance.

Our study has some limitations. First, its retrospective design and sample size limit the strength of the conclusions. Second, although this study considers a recruitment of participants at a community center, we cannot exclude the possibility of a selection bias. This may occur because some patients may not have been identified by public health services as tuberculosis contact patients and therefore were not included in our sample. Considering that this should represent a small number of patients, this bias is expected to have a minimal effect on the results. Finally, some factors found in other studies as determinants of compliance, such as parents' education[15] and cultural beliefs were not assessed in this study.

Conclusions

PT compliance was largely increased after implementation of improvement strategies. Non-compliance was

Table 1 Sociodemographic and clinical characteristics.

Variable	Total group $n=72$	Compliance $n=46$	Non-compliance $n=26$	p-Value
Age, years, mean ± SD	5.5 ± 4.2	4.8 ± 3.8	6.9 ± 4.7	0.046
Male, No. (%)	40 (55.6)	29 (63.0)	11 (42.3)	0.089
Index case				
Mother, No. (%)	12 (16.7)	7 (15.2)	5 (19.2)	0.746
Father, No. (%)	9 (12.5)	7 (15.2)	2 (7.7)	0.473
Brother/sister, No. (%)	2 (2.8)	0 (0)	2 (7.7)	0.127
Grandparents, No. (%)	20 (27.8)	14 (30.4)	6 (23.1)	0.503
Uncle/aunt, No. (%)	14 (19.4)	8 (17.4)	6 (23.1)	0.558
Other, No. (%)	10 (13.9)	7 (15.2)	3 (11.5)	0.739
No index case identified, No. (%)	5 (6.9)	3 (6.5)	2 (7.7)	0.999
Contact with index case[*]				
Daily, No. (%)	35 (63.6)	22 (61.1)	13 (68.4)	0.592
Weekly, No. (%)	11 (20.0)	8 (22.2)	3 (15.8)	0.730
Sporadic, No. (%)	9 (16.4)	6 (16.7)	3 (15.8)	0.999
Tuberculosis of the index case[†]				
Pulmonar, No. (%)	59 (92.2)	36 (87.8)	23 (100)	0.150
Pleuropulmonar, No. (%)	3 (4.7)	3 (7.3)	0 (0)	0.547
Miliar, No. (%)	2 (3.1)	2 (4.9)	0 (0)	0.532
M. tuberculosis of the index case[‡]				
Susceptible to all drugs, No. (%)	54 (90.0)	33 (86.8)	21 (95.5)	0.400
Resistant to isoniazid, No. (%)	5 (8.3)	4 (10.5)	1 (4.5)	0.643
Multidrug resistant, No. (%)	1 (1.7)	1 (2.6)	0 (0)	0.999
Drug of choice, No. (%)				
Isoniazid	67 (93.1)	42 (91.3)	25 (96.2)	0.647
Rifampicin	5 (6.9)	4 (8.7)	1 (3.8)	0.647
Origin of the patient, No. (%)				
Public health	61 (84.7)	39 (84.8)	22 (84.6)	0.999
Family doctor	4 (5.6)	3 (6.5)	1 (3.8)	0.999
Emergency department	1 (1.4)	1 (2.2)	0 (0)	0.999
Oncology department	1 (1.4)	0 (0)	1 (3.8)	0.361
Pediatrician appointment	4 (5.6)	3 (6.5)	1 (3.8)	0.999
Inpatient department	1 (1.4)	0 (0)	1 (3.8)	0.361
Reason for referral, No. (%)				
Exposure to TB	63 (87.5)	39 (84.8)	24 (92.3)	0.473
Suspicion of active TB	5 (6.9)	4 (8.7)	1 (3.8)	0.647
Candidate to immunosuppressive treatment	4 (5.6)	3 (6.5)	1 (3.8)	0.999
Type of preventive therapy, No. (%)				
CP	33 (45.8)	25 (75.8)	8 (24.2)	0.054
LTBI treatment	39 (54.2)	21 (53.8)	18 (46.2)	0.054
Family disfunction, No. (%)	10 (13.9)	0 (0)	10 (38.5)	[§]
Medication problems, No. (%)	10 (13.9)	0 (0)	10 (38.5)	[§]

SD: standard deviation; CP: chemoprophylaxis; LTBI: latent tuberculosis infection.
[*] 17 missing values (10 in the compliance group; 7 in the non-compliance group).
[†] 8 missing values (5 in the compliance group; 3 in the non-compliance group).
[‡] 12 missing values (8 in the compliance group; 4 in the non-compliance group).
[§] Not possible to compute.

associated with older age of patients. There was no significant difference in treatment compliance between rifampicin and isoniazid. A 9-month regimen with isoniazid continues to be the preferred modality for LTBI treatment. Compliance can be greatly improved by close monitoring and strategies to reconnect families with the PT, rather than shortening of treatment regimens. We emphasize the importance of health facilities inside

the community, with experience in tuberculosis in children.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Carvalho A, Carvalho I, Marques L, Duarte R. Consenso sobre a abordagem da criança exposta a doente com tuberculose. Acta Pediatr Port. 2014;45:242–51.
2. Marais BJ. Improving access to tuberculosis preventive therapy and treatment for children. Int J Infect Dis. 2017;56:122–5.
3. Kendall EA. Tuberculosis in children: under-counted and under-treated. Lancet Glob Heal. 2017;5(9):e845–6.
4. DGS. Norma nº 006/2016 de 29/06/2016: Estratégia de vacinação contra a tuberculose com a vacina BCG; 2016.
5. Singh V, Patra S. A relook at preventive therapy for tuberculosis in children. Indian J Pediatr. 2011;78(2):205–10.
6. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection – the promise and the challenges. Int J Infect Dis. 2017;56:68–76.
7. Pina-gutiérrez JM, Ferrer-traid A, Arias C, Meses D, Una EN, Pacientes CDE. Cumplimiento y efectividad del tratamiento de la infección tuberculosa con isoniazida durante 9 meses en una cohorte de 755 pacientes. Med Clin (Barc). 2008;130(5):165–71.
8. McClintock AH, Eastment MK, McKinney CM, Pitney CL, Narita M, Park DR, et al. Treatment completion for latent tuberculosis infection: a retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. BMC Infect Dis. 2017;17(1):1–8.
9. Sterling TR, Villarino E, Borisov AS, Shang N, Gordin F, Bliven-sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011:2155–66.
10. Lamb GS, Starke JR. Tuberculosis in infants and children. Microbiol Spectr. 2017;5(2):422–33.
11. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007;45:715–22.
12. Health IC. Missed opportunities for prevention of tuberculosis in children. Ann Trop Paediatr. 2011;31(4):297–9.
13. Guix-Comellas EM, Rozas L, Velasco-Arnaiz E, Morín-Fraile V, Force-Sanmartín E, Noguera-Julian A. Adherence to antituberculosis drugs in children and adolescents in a low-endemic setting: a retrospective series. Pediatr Infect Dis J. 2017;36(6):616–8.
14. Carvalho I, Goletti D, Manga S, Silva DR, Manissero D, Migliori G. Managing latent tuberculosis infection and tuberculosis in children. Rev Port Pneumol. 2018;24(2):106–14.
15. Singh AR, Kharate A, Bhat P, Kokane AM, Bali S, Sahu S, et al. Isoniazid preventive therapy among children living with tuberculosis patients: Is it working? A mixed-method study from Bhopal, India. J Trop Pediatr. 2017;63(4):274–85.
16. Belgaumkar V, Chandanwale A, Valvi C, Pardeshi G, Lokhande R, Kadam D, et al. Barriers to screening and isoniazid preventive therapy for child contacts of tuberculosis patients. Int J Tuberc Lung Dis. 2018;22(10):1179–87.
17. Garie KT, Yassin MA, Cuevas LE. Lack of adherence to isoniazid chemoprophylaxis in children in contact with adults with tuberculosis in Southern Ethiopia. PLoS One. 2011;6(11):1–4.

Pulmonol. 2020;**26(2)**:84–89

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Organization of Home Mechanical Ventilation in Portugal: Characterization of current centers and a pathway to uniformization

M.A. Mineiro[a,*], M.J. Guimarães[b], J.C. Winck[c]

[a] *Pulmonology Department. Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal*
[b] *Pulmonology, Hospital da Luz Guimarães, Guimarães, Portugal*
[c] *Pulmonology, Faculty of Medicine, Porto University, Portugal*

Received 28 February 2019; accepted 1 May 2019
Available online 1 June 2019

KEYWORDS
Home Mechanical Ventilation;
Organization;
Survey

Abstract
Introduction: Home Mechanical Ventilation (HMV) is increasing worldwide.
Objective: Characterization of the Portuguese HMV Units.
Methods: The HMV Team Group of the Portuguese Pulmonology Society prepared a questionnaire that was sent by e-mail addressed to Pneumology Department Directors throughout the country, and the responses were then analyzed. The results enabled a provisional classification of the Units, which followed specific criteria.
Results: Thirty centers were surveyed, of which 60% (18) sent the answers to the questionnaire. As for the results obtained, only one center was considered as a basic unit. Most centers (14/18) were considered specialized units. 3/18 centers were classified as highly complex multidisciplinary units. Of the 12 centers that did not answer the questionnaire, one refused to do it and another center was in transition period.
Conclusions: Analysis of the results reveals the high number of patients treated with HMV in Portugal, supports the importance of creating protocols to standardize HMV countrywide, and audit its practice through the creation of a national register.

* Corresponding author.
E-mail address: xmineiro@gmail.com (M.A. Mineiro).

https://doi.org/10.1016/j.pulmoe.2019.05.006

Introduction

The number of patients under Home Mechanical Ventilation (HMV) is growing worldwide[1,2] and organization is crucial.

Organization varies widely in Europe; for example in Denmark, where patients were referred to only two Respiratory Care units (RCU), or in Sweden where there were a wide number of outpatient clinics caring for the patients and reporting them to a national HMV register, owned by the Swedish Society of Chest Medicine and financially supported by another health institution.[3]

The creation of national registries and databases on COPD, respiratory failure or Home Mechanical Ventilation (HMV), along with specific surveys, clarifies the practices and leads to improvement in patient management.[4–6]

It is essential to know more about the current situation in Portugal to plan for the ideal resources. In 1996, in Portugal, there was a prevalence of 2.7 patients under HMV per 100.000 inhabitants.[7]

In 2001, data from the Eurovent survey[8] confirmed the existence of 801 patients in Portugal with an estimated prevalence of 9.3 patients under HMV per 100.000 inhabitants. Out of 34 prescribing centers identified, 20 centers participated in the survey, with a mean number of 21 patients per center.

With the objective of characterizing Home Mechanical Ventilation (HMV) Centers in Portugal, a specific questionnaire was prepared and sent to all Heads of Department of Pulmonology Units in public Hospitals. It was based on the Spanish Society of Pulmonology (SEPAR) criteria.[9,10]

Material and methods

The Home Mechanical Ventilation Team Group of the Portuguese Pulmonology Society conducted an observational study in public hospitals in Portugal in the last trimester of 2018.

The questionnaire covered several areas, asking about the practice of noninvasive ventilation (NIV) in both acute and chronic setting. These areas included assistance activities, technical and human resources, accredited training in ventilation, teaching activity, research activity and representative activities.

Analysis of the answers produced a provisional classification of the Units, of increasing complexity. At each level there was a definition of essential or required criteria, and recommended criteria (these for a later definition of excellence, which was not an objective of the present study). At the highest level most of the criteria were obligatory. The classification was as follows:

- **Basic unit**: number of new patients per year >10 or total number of patients treated >40; availability of pulse oximetry and spirometer.
- **Specialized unit**: number of new patients per year >20 or total number of patients treated >100 and, beyond the criteria defined above: possibility of urgent ambulatory care (in less than 15 days); specific consultation on NIV or chronic respiratory failure; pulse oximetry and patient monitoring available, plus evaluation of cough strength. Patient monitoring under NIV included heart rate, respiratory rate, blood pressure and oxygen saturation (SaO_2). In addition, there should be the existence of written care protocols on NIV and at least one publication per year in journals with impact factor.

  Equipment for lung function tests (with muscular pressures measurement) and/or sleep study are desirable, as well as appropriate human resources (one full-time doctor, nurse and physiotherapist), but not mandatory.

  It was also recommended that some of the staff members should belong to the national HMV or Sleep Pathology assemblies, coordinated by the Portuguese Pneumology Society.
- **High complexity multidisciplinary unit**: number of new patients per year >30 or total number of patients >200 and, beyond the criteria defined above: unit of respiratory care or own beds with patient monitoring; requirement of complete equipment for lung function tests (with muscular pressures measurement) and sleep study (full polysomnography under ventilation); adequate monitoring including transcutaneous capnography; adequate human resources (2 doctors, 1 nurse, 1 physiotherapist or cardiopneumologist) and presence of at least one PhD qualified doctor on the medical team. Staff members should dedicate at least 80% of their time to NIV. Furthermore, there should be regular training activities and an in-home care program. Regular training activities included participation of staff members as trainees on HMV accredited courses (by independent organizations), in the previous 5 years.

Coordinated activity with the services of Neurology/Neurophysiology, Cardiology, Endocrinology/Dietitian, Otolaryngology, Gastro and Palliative Care is mandatory at this level. The same applies to the existence of a specific resident program on NIV, and the presence of PhD holders on the staff.

As for research activities (clinical trials, etc.), investigation and liaison to a Faculty, they remained as recommended criteria at this level too (Tables 1 and 2).

Once all the surveys were collected, and, whenever there was doubt in the classification to be assigned (given the heterogeneity of existing resources), casuistic data and technical differentiation were favored.

Results

Thirty centers were surveyed, from North to South of the country, through direct contact to the Service Directors, of which 60% (18) sent the answers to the questionnaire (Table 3).

Only one center from the results obtained was considered to be a basic unit and that was due to the scarcity of technical resources. However, it should be noted that the number of new patients per year was >30, and total number of patients was >200.

Most centers (14/18) were considered specialized units. Of these, the majority (8/14) reported new patients >30/year and total >200/year. Moreover, 8/14 centers reported having their own beds for ventilatory support, which were also criteria for a more differentiated unit.

In some units not all the essential criteria were met: one center did not have urgent ambulatory care, another one

Table 1 Original survey.

Serviço de Pneumologia: _____	Unidade de VMD - Nível: _____
I. Actividade Assistencial	
1.1. N° de doentes novos/ano tratados com ventilação mecânica domiciliária (VMD)	>10/20/30
1.2. N° total de doentes tratados na Unidade com VMD	>40/100/200
2. UCRI ou camas próprias com monitorizacão	Sim/Não
3. Possibilidade de início de VNI em doente internado ou ambulatório	Sim/Não
4. Possibilidade de atendimento urgente ambulatório (15d)	Sim/Não
5. Actividade coordenada com os serviços de Neurologia/Neurofisiologia, Cardiologia, Endocrinologia/Dietista, MFR, ORL, Gastro e C. Paliativos	Sim/Não
II. Recursos Técnicos	
6. Organigrama de funcionamento estável	Sim/Não
7. Espaço físico (sala de observações, quartos de ambulatório de VMD, secretária, sala de espera) para a atividade	Sim/Não
8. Consulta detalhada de VMD	Sim/Não
9. Monitorização noturna sob ventilação: Oximetria de pulso	Sim/Não
10. Monitorização noturna sob ventilação: pCO_2 transcutâneo	Sim/Não
11. Monitorização sob ventilação: FC, FR, TA, SaO_2	Sim/Não
12. Capacidade de análise do software do ventilador	Sim/Não
13. Capacidade de Polissonografia completa sob Ventilação	Sim/Não
14. Programa de atendimento no domicílio	Sim/Não
15. Estudo funcional respiratório completo incluindo estudo de pressões musculares	Sim/Não
16. Avaliação da eficácia da tosse	Sim/Não
17. Protocolos assistenciais	Sim/Não
III. Recursos humanos	
18. N° de médicos Pneumologistas no staff da unidade (n° mínimo a tempo completo)	-
19. N° de enfermeiras, técnicos (ou similar) especializada na unidade a tempo completo	-
20. N° de fisioterapeutas especializados na unidade	-
21. Pneumologista de chamada em presença física	-
IV. Formação creditada em VMD (algum dos membros da unidade foi aluno)	
22. Participação em cursos creditados por sociedades independentes da SPP ou internacionais	Sim/Não
V. Atividade Docente (nos 5 anos anteriores)	
23. Formação de internos com programa e rotação específica em VMD	Sim/Não
24. N° de cursos de pós-graduação realizados pela unidade (n° mínimo)	-
25. N° de membros da unidade doutorados	-
26. N° de professores da Universidade (catedráticos, titulares e auxiliares) que constam entre os membros da Unidade (n° mínimo)	-
VI. Atividades ligadas a Investigação (nos 5 anos naturais prévios ao ano de solicitação)	
27. N° de trabalhos originais relacionados com ventilação e publicados em revistas com FI (n° mínimo)	-
28. Nº de projetos financiados pela SPP, FCT ou Universidades	-
29. N° de ensaios clínicos em VMD	-
VII. Atividade Representativa (alguns dos membros da unidade, sem limite temporal)	
30. Pertencer a Comissões de Trabalho de Ventilação Domiciliária ou de Patologia do Sono	Sim/Não

had no written protocols and another center lacked appropriate monitoring during NIV (heart rate, blood pressure, or SaO_2). Only 5/14 centers reported that they had published, as required and in the previous year, original articles related to ventilation in journals with an impact factor.

4/14 centers reported not having any kind of full-time staff dedicated to NIV (though it was not an essential criterion for this unit level). However, the other 10/14 centers had mainly 1 (in 6 centers) dedicated pulmonologist on the staff, 1–4 nurses or technicians. One center reported 9 technicians. Only 5/14 centers had 1–2 physiotherapists (Table 4).

All the centers reported regular accredited training but only 3/14 reported having one PhD holder on the staff.

Interestingly, only one center reported that initialization and NIV titration in chronic patients was usually done under polysomnography, and during daytime.

Out of all centers, 3/18 were classified as highly complex multidisciplinary units. In general, all the technical resources were present. But only 1/3 centers had a specific

Table 2 Survey.

Pneumology Department: _____	HMV Unit Level: _____
I. Assistance Activities	
1.1. No. of new patients per year >10	>10/20/30
1.2. Total number of patients treated >40	>40/100/200
2. Unit of respiratory care or own beds with patient monitoring	Yes/No
3. Possibility of beginning HMV in hospital or as outpatient	Yes/No
4. Possibility of emergency care (15d)	Yes/No
5. Coordinated activity with the services of Neurology/Neurophysiology, Cardiology, Endocrinology/Dietitian, Physiatry, Otolaryngology, Gastro and Palliative Care	Yes/No
II. Technical Resources	
6. Stable operating organization chart	Yes/No
7. Dedicated NIV physical space (observation room, desk, waiting room)	Yes/No
8. Detailed medical consultation	Yes/No
9. Nocturnal monitorization under ventilation: Pulse oximetry	Yes/No
10. Nocturnal monitorization under ventilation: transcutaneous CO_2	Yes/No
11. Monitoring ventilation: HR, RR, BP, SaO_2	Yes/No
12. Analysis of the ventilator software data	Yes/No
13. Full Polysomnography Ability under Ventilation	Yes/No
14. In-home care program	Yes/No
15. Equipment for lung function tests with respiratory muscles pressures measurement	Yes/No
16. Evaluation of cough strength	Yes/No
17. Written protocols on NIV	Yes/No
III. Human Resources	
18. Number of physicians – Pulmonologists – on the unit staff (full-time minimum)	–
19. Number of nurses, technicians (or similar) specialized in full time unit	–
20. Number of physiotherapists specialized in units	–
21. Pulmonologist on-call	–
IV. Regular accredited training	
22. Participation in courses accredited by independent organizations (national or international)	Yes/No
V. Teaching activities (in the last 5 years)	
23. Resident training, with specific program for NIV	Yes/No
24. Number of postgraduate courses offered by the department	–
25. Number of PhD members in staff	–
26. Number of University members in staff	–
VI. Research activities (in the last 5 years)	
27. Number of published articles, related to NIV	–
28. Number of projects with financial support from Portuguese Society of Pulmonology or by the University	–
29. Number of clinical trials in NIV	–
VII. Representative activities (some of the unit members, no time limit)	
30. Belonging to local executive committee on HMV	Yes/No

Abbreviations: HMV: Home Mechanical Ventilation; NIV: noninvasive ventilation; HR: heart rate; RR: respiratory rate; SaO_2: oxygen saturation.

home care program in addition to what is regularly provided by home-based care companies. The two other centers stated that a similar program was in construction or awaiting approval.

Regarding human resources, 2/3 had a full-time pulmonologist (more than 80% time dedicated to ventilation therapies). There were 3 nurses and 8 technicians in one center; one nurse in another; and 6 nurses in partial time in the last one. None of the centers had a full-time physiotherapist. Thus, strictly speaking, none of the centers fulfilled the rigorous essential criteria for human resources.

Teaching activities were regularly provided in all centers, as required.

In all 3 centers there was one PhD member that also belongs to a Faculty.

Concerning research activities only one center had a clinical trial as well as several investigation projects going on.

For the 12 centers that did not answered to the questionnaire, one refused to do it; another center did not respond due to logistical reasons. As for the remaining 10 centers, it was assumed that they essentially corresponded to basic units or centers where ventilation in respiratory failure is

Table 3 HMV units classification and response rate.

Final classification ($n = 30$)	n
Basic unit	1
Specialized unit	14
Highly complex multidisciplinary units	3
Units classified	18 (60%)
Refused	1
Transition period	1
No answer	10
Units that didn't respond	12 (40%)

Table 4 Human resources in specialized units.

Specialized units ($n = 14$)	None	1 or more (maximum of 4)
Full-time pulmonologist	4	10
Full-time nurse or technician	4	11
Full/partial-time physiotherapist	8	5

performed by specialists in other fields, as the medical staff was known to be reduced (one or two permanent pneumologists).

Finally, about technical resources among the total number of centers, it is worth noting that 11/18 mentioned the possibility of performing transcutaneous capnography, and 16/18 reported full polysomnography ability under ventilation.

Discussion

Considering the casuistic SEPAR criteria (number of new patients per year and total number of patients per year), from the Eurovent Survey in 2001: only one (with 217 patients) met a high-complexity HMV center classification, and another one (with 100 patients) met specialized HMV center criteria; considering only the first criteria (number of new patients per year) there were 3 classified as high-complexity HMV centers (with at least 30 new patients treated the last year); and 8 classified as Basic HMV units (with less than 20 patients but at least 10).

The analysis of the results highlights the high number of patients treated with HMV in Portugal and compared with 2001 there is an increase in the expertise of the centers surveyed.

We found that most of the centers (11/18) reported having dedicated NIV rooms, meaning that awareness of NIV limitations and risks is present. This is important as NIV should not be delivered in general wards, which cannot provide proper monitoring.

However, in a worldwide web-based survey focused on NIV use in general wards, it was found that the percentage of hospitals using NIV in wards is increasing and reached 66% of the centers studied.[11] Monitored beds are often unavailable, forcing physicians to manage acute respiratory failure in suboptimal settings.

In our study, the scarcity of staff specialized in NIV administration – including doctors, nursing and other technicians – was evident. The physiotherapist usually covers several departments in the hospital, daily. Also, nurses can specialize in pulmonary rehabilitation.

Considering technical resources, we found that equipment like capnography and polysomnography are widely used but organized units of respiratory care are missing.

Another point refers to home care programs. They are provided, up to a certain point, by the companies, along with NIV equipment distribution. Real home care hospital based programs are lacking.

Also, most centers (16/18) had written protocols on NIV. This is impressive because other authors found that only 50% of the respiratory medicine departments had written protocols.[12] Protocols may help to optimize health care procedures. Published articles, investigation and research network with universities are growing but varies greatly between institutions.

Our evaluation of the HMV laboratories has limitations, such as the absence of questions to evaluate the number of patients treated according the specific pathology (COPD, restrictive, neuromuscular, etc.). The different practices were not discriminated, such as the ventilator type or how to titrate ventilation. The questionnaire was primarily intended to assess patients with respiratory insufficiency, but the number of patients referred may, in some cases, include pure obstructive sleep apnea.

Conclusion

It is possible to say that, in Portugal, HMV encompasses a relevant number of patients treated per year. The heterogeneity of the resources, both technical and human, is very marked. Finally, the need to standardize HMV practices and audit its practice through the creation of a national register is clearly required.

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. Povitz M, Rose L, Shariff SZ, Leonard S, Welk B, Jenkyn KB, et al. Home mechanical ventilation: a 12-year population-based retrospective cohort study. Respir Care. 2018;63(4):380–7.
2. Hill NS. The worldwide spread of noninvasive ventilation; too much, too little or just right? Tanaffos. 2013;12:6–8.
3. Midgren B, Olofson J, Harlid R, Dellborg C, Jacobsen E, Norregaard O. Home mechanical ventilation in Sweden, with reference to Danish experiences. Respir Med. 2000;94:135–8.
4. Lange P, Tottenborg SS, Sorknaes AD, Andersen JS, Sogaard M, Nielsen H, et al. Danish Register of chronic obstructive pulmonary disease. Clin Epidemiol. 2016;8:673–8.

5. Tollefsen E, Midgren B, Bakke P, Fondenes O. Amyotrophic lateral sclerosis: gender differences in the use of mechanical ventilation. Eur J Neurol. 2010;17(11):1352–7.
6. Rose L, McKim A, Katz SL, Leasa D, Nonoyama M, Pedersen C, et al. Home Mechanical Ventilation in Canada: a national survey. Respir Care. 2015;60:695–704.
7. Winck JC, on behalf of the HMV Sub-group of the Respiratory Rehabilitation Committee of the SPP. Normas e Recomendações da Ventiloterapia domiciliária. Rev Port Pneumol. 1998;IV:447–78 [in Portuguese].
8. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005;25:1025–31.
9. Terán Santos J. Accreditation for units treating sleep disorders in respiratory medicine. Arch Bronconeumol. 2009;45:263–5.
10. Márquez Pérez FL, Capelastegui Saiz A. Acreditación SEPAR de unidades monográficas Qué nos dice RECALAR. Monogr Arch Bronconeumol. 2018:00155 http://separcontenidos.es/revista/index.php/revista/article/view/231/379
11. Cabrini L, Esquinas A, Pasin L, Nardelli P, Frati E, Pintaudi M, et al. An international survey on noninvasive ventilation use for acute respiratory failure in general non-monitored wards. Respir Care. 2015;60:586–92.
12. Chiner Eusebi, Llompart Mónica, Martinez-Garcia Miguel Angel, Fernandez-Fabrellas Estrella, Navarro Rafael, Cervera Angela, et al. Noninvasive mechanical ventilation in Valencia, Spain: from theory to practice. Arch Bronconeumol. 2009;45:122–6.

Pulmonol. 2020;**26(2)**:90–94

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Tracheostomy prevalence at Skilled Nursing Facilities

F. Pereira[a,*], A.Maia Silva[a], I.Machado Vaz[b], S. Viamonte[b], J.C. Winck[b]

[a] *Hospital Senhora da Oliveira - Guimarães, Portugal*
[b] *Centro de Reabilitaçao do Norte, Portugal*

Received 8 April 2019; accepted 23 May 2019
Available online 22 June 2019

KEYWORDS
Tracheostomy;
Ventilatory weaning;
Skilled Nursing Facilities

Abstract The incidence of chronically ill subjects with prolonged mechanical ventilation has significantly increased over the last decade. Many patients get discharge to Skilled Nursing Facilities with an artificial airway, which do not have the means to properly progress on weaning. In Portugal this prevalence is unknown. Our aim was to establish the prevalence of tracheostomized patients at SNF in the North of Portugal, characterizing these units and its population, in a cross-sectional study, through an online questionnaire answered on the same day. Of the 75 SNF, 30 answered: 13 long-term, 2 medium-term, 2 short-term, 12 had beds of both medium and long-term and 1 had the three typologies. 33 had tracheostomy ventilation (prevalence 3.36%), all admitted at long-term units, the majority transferred from previous hospital admission ($n = 27$, 90%). Only one was under mechanical ventilation. The most frequent reason for tracheostomy placement was acute respiratory failure ($n = 10$, 33.3%). The most commonly presented cannula was the fenestrated non-cuffed ($n = 17$, 59%). Only 4 were performing occlusion training, 21 needed frequent secretion suctioning and 1 used the mechanical in-exsufflation. Regarding motor function, 16 (53.3%) were unable to achieve sitting balance and 20 (66.7%) had no orthostatic balance or walking ability. 14 (46.7%) had percutaneous endoscopic gastrostomy. Although low response rate may induce some bias, this study revealed a significant prevalence of tracheostomized patients at SNF. These facilities do not have the resources to safely and effectively progress on ventilatory weaning. It is essential to establish new referral criteria and create specialized weaning units.

Introduction

Mechanical ventilation (MV) is the most commonly used technique for short-term life support worldwide, and it is

* Corresponding author.
E-mail address: filipacarvalhopereira@gmail.com (F. Pereira).

https://doi.org/10.1016/j.pulmoe.2019.05.011

used in daily practice for a diverse spectrum of indications.[1] An increasing number of patients are undergoing this technique due to demographic changes (aging populations with more comorbidities) and a greater incidence of respiratory and cardiovascular pathologies.[2] Improved intensive care unit (ICU) care has resulted in many patients surviving acute respiratory failure and requiring prolonged MV during recovery.[3]

Endotracheal tubes and tracheostomies are both considered as artificial airways. Approximately 10% of critically ill patients receive a tracheostomy in order to facilitate weaning from prolonged MV support. The decision to perform the technique is predominantly based on the predicted duration of MV. Tracheostomy has some advantages, such as better tolerance, simpler bedside procedures, little or no need for sedation, allowing oral feeding and phonation, and facilitating lung volume recruitment and mechanically assisted cough techniques. Although it decreases time until discharge from the ICU, the duration of decannulation ends up being prolonged.[4–7] When patients are no longer in the acute phase and clinical stability is achieved, they can be discharged from the ICU to medical or surgical wards.[2,8] Tracheostomy allows them to be transferred to other step-down units.[6]

It has been claimed that ICUs are expensive, but an unguided ventilatory weaning process has higher medium to long-term economic costs, and above all, it is associated with lower quality of life, higher morbidity, and mortality.[2,7,8]

After hospital discharge, many tracheostomized patients are admitted to intermediate-care facilities in order to release hospital beds and continue their rehabilitation process before returning home. This also improves patient independence, recovery of physical condition, and ventilatory weaning.[9]

A multidisciplinary tracheostomy team is recommended to facilitate ventilatory weaning and should include physicians, nurses, physiotherapists (PT), speech and language therapists (SLT), occupational therapists (OT), nutritionists, psychologists, and social workers.[2,5]

Patients with prolonged weaning are frequently transferred from acute-care hospitals to Skilled Nursing Facilities (SNFs). These facilities do not have the means, experienced multidisciplinary teams, or medical equipment to carry out weaning or decannulation safely and effectively.

In Portugal, the number of tracheostomized patients admitted to SNFs remains unknown. The aim of this study was to conduct a questionnaire at SNFs in the north of Portugal and establish the prevalence of patients who need tracheostomy ventilation. The facilities' characteristics and tracheostomized populations are also described.

Material and methods

Study design

This study had a one-day cross-sectional design. An online questionnaire was sent to SNFs in the northern region of Portugal and used to collect data.

Ethical considerations

The questionnaire was developed by the research group and approved by the Ethical Committee of Santa Casa da Misericordia do Porto, Portugal. The patients were anonymized, and no intervention was planned. Very little time was needed to complete the questionnaire, and it did not have any implications for patient care.

Data collection and statistical analysis

Initially, all SNFs in the north of Portugal were identified, and an online questionnaire was sent to each facility. The questionnaire was related to the same specific day for all units to prevent the risk of the same patient being included more than once or excluded in cases of patient discharge. The study was conducted on October 12, 2017.

The questionnaire had two parts: one referring to SNF characteristics and another about each tracheostomized patient that was admitted to the facilities (other patients were not analyzed).

For each SNF, we collected baseline data, including the type of SNF typology (short-term units for patients admitted for 31 days, medium-term units for 90 days, or long-term units for more than 90 days), and the number of beds per facility. We also recorded the number of Physical and Rehabilitation Medicine physicians (responsible for patient diagnosis and treatment, as well rehabilitation process coordination using multi-professional team), PT (who aim to restore, either in full or in part, patients' movement and functional ability), OT (work with activities to achieve maximum independence in daily life), and SLT (help with speech, language and swallowing problems) worked hours per week.

For each patient requiring tracheostomy ventilation, we collected data that included demographics, the hospital admission date, the primary medical diagnosis, the date and reason for the tracheostomy, the SNF admission date, the consciousness evaluation using the Glasgow Coma Scale (GCS), respiratory support (the type of tracheostomy cannula, ventilator/oxygen supply, cough assistance, secretion suctioning), feeding evaluation, neuromotor evaluation (control balance in seated and orthostatic positions, walking ability), skin evaluation (number and type of ulcers).

The results of the questionnaires were given to the same researcher after they were completed. The data were analyzed using SPSS v23 and descriptive statistics. Only variables with complete data were analyzed. Numbers, percentages, means, and the distributions of minimum and maximum values were used to evaluate descriptive data.

Results

The online questionnaire was sent to 75 SNFs, and responses were obtained from 30 facilities. Table 1 summarizes the information obtained about SNF characteristics. The majority were medium and medium/long-term units ($n = 25$; 83.3%). Overall, long-term units had more admitted patients (mean 26.7 patients). All facilities except one had a Physical and Rehabilitation Medicine (PRM) physician coordinating the rehabilitation care. All 30 facilities had a PT, 28 had an OT, and 26 had an SLT in their unit.

Table 1 Description of SNFs characteristics (SNF: Skilled Nursing Facility; PRM: Physical Rehabilitation and Medicine, FT: Physiotherapy; OT: Occupational Therapy; SLT: Speech and Language Therapy).

Type of SNF	Number of units	Bed capacity per unit (mean)	Number of PRM Physician hours/week	Number of PT hours/week	Number of OT hours/week	Number of SLT hours/week
Short-term unit	2 (6.7%)	19	7.75	110	30.5	12.5
Medium-term unit	2 (6.7%)	26	10	75	35	7
Long-term unit	13 (43.3%)	28	4.8	35	27	4.6
Medium/long-term unit	12 (40%)	16/22	5.25	67.3	19.6	12.8
Short/medium/long-term unit	1 (3.3%)	14/18/32	11	108	65	9

Table 2 Demographic and clinical characteristics (SNF: Skilled Nursing Facility).

Description	*n* (%)
Age (mean)	65.2 years
Gender	
Male	18 (60%)
Female	12 (40%)
Hospitalization before SNF admission	
Yes	27 (90%)
No, from home	2 (6.7%)
No, from another facility	1 (3.3%)
Primary diagnosis for admission	
Stroke	9 (30%)
Tumor (laryngeal/tongue cancer)	8 (26.7%)
Acute respiratory failure	3 (10%)
Anoxic encephalopathy	3 (10%)
Spinal cord injury	2 (6.7%)
Amyotrophic Lateral Sclerosis	1 (3.3%)
Cerebral palsy	1 (3.3%)
Sudden Cardiac Arrest	3 (10%)
Reason for tracheostomy	
Acute respiratory failure	10 (33.3%)
Postoperative care	3 (10%)
Neuromuscular disease	1 (3.3%)
Stroke	8 (26.7%)
Cardiovascular disease	2 (6.7%)
Other	6 (20%)

regard to the time spent at the facilities, short and medium-term units had the highest amount of support from PRM physicians. Long-term units had the lowest support with fewer hours per week from PT, OT and SLT to treat their patients. Generally, the SNFs were understaffed and with a low ratio of therapists to patients. Four units did not have SLT, which are important for tracheostomized patients for managing communication and swallowing disorders.

Among all SNFs, 33 patients had undergone tracheostomies. Three were excluded because of incomplete questionnaires. The demographic information of the patients requiring tracheostomy ventilation is provided in Table 2. The average age was 65.2 years and ranged from 18 to 91 years. There were 12 (40%) female and 18 (60%) male patients. All of them were adults and institutionalized at long-term units. The majority were admitted after hospital discharge ($n = 27$, 90%).

Overall, the most frequent diagnoses for admission were stroke and laryngeal or tongue cancer ($n = 17$, 56.7%). The indications for tracheostomy were divided into six categories: acute respiratory failure, postoperative care, neuromuscular disease, stroke, cardiovascular disease, and other reasons. The most common cause was acute respiratory failure ($n = 10$, 33.3%). Most tracheostomies ($n = 20$, 66.7%) were performed during the first and second week after hospital admission. The mean time between tracheostomy placement and SNF admission was 74.9 days.

Fig. 1 shows that the majority of patients had a non-cuffed fenestrated tube ($n = 9$, 30%). Four (13.3%) needed O_2 supplementation via tracheostomy tube (1.5–8 l/min). One needed ventilatory support (a patient with laryngeal cancer). Only 4 patients were progressing in ventilatory weaning and undergoing occlusion training. In addition, only one had a mechanical in-exsufflation, but 21 patients (70%) needed tracheal suctioning (1–6 times per day). This suggests that mechanical cough assistance was probably necessary but was not available.

Table 3 summarizes the levels of consciousness (using the GCS), feeding evaluation, neuromotor evaluation, and skin assessment of the sample at the same point in time. According to the CGS, 14 patients scored below 8 points, 6 patients scored between 9 and 12 points, and 10 patients scored higher than 10 points. A high percentage of subjects were being fed enterally, including 14 (46.7%) who had had a percutaneous endoscopic gastrostomy (PEG) and 11 (36.7%) who had a nasogastric tube (NGT). More than half of the patients were unable to maintain sitting balance (53.3%) and more were unable to stand or walk (66.7%). There were 16 bedridden patients (53.3%). A minority had pressure ulcers ($n = 4$, 13.3%), including one case of grade I, one case of grade II, and two cases of grade IV. None were on a dialysis program.

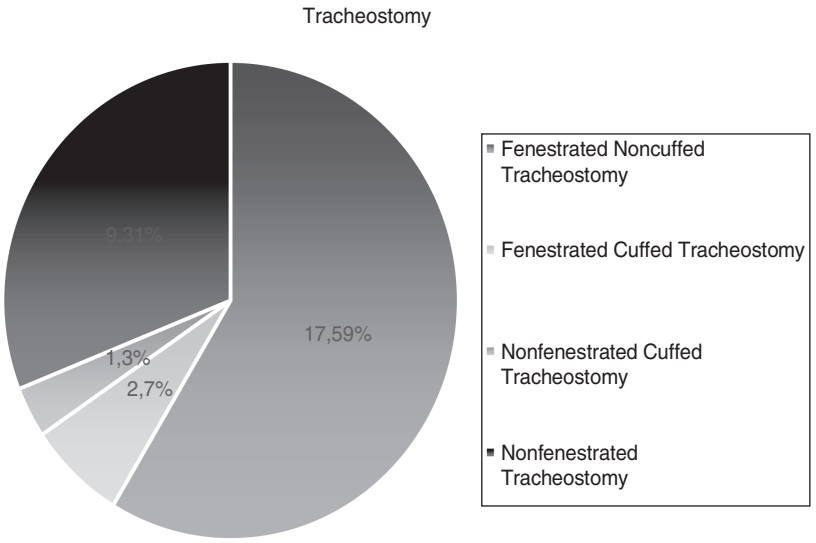

Figure 1 Types of tracheostomy tubes used at SNFs.

Table 3 Level of consciousness, feeding/neuromotor evaluation and skin assessment of tracheostomized patients (reported at the same time point).

Description	Frequency, *n* (%)
Level of consciousness – Coma Glasgow Scale	
3–8 (severe)	14 (46.7%)
9–12 (moderate)	6 (20%)
13–15 (mild)	10 (33.3%)
Feeding	
Oral (without restrictions)	1 (3.3%)
Oral (thickened liquids)	2 (6.7%)
Percutaneous endoscopic gastrostomy (PEG)	14 (46.7%)
Nasogastric tube (NGT)	11 (36.7%)
PEG + oral training	1 (3.3%)
Sitting balance	
Good (static and dynamic)	6 (20%)
Good (only static)	5 (16.7%)
Fair	1 (3.3%)
Poor	2 (6.7%)
Absent	16 (53.3%)
Orthostatic balance	
Good	7 (23.3%)
With walking device	1 (3.3%)
With third-person aid	2 (6.7%)
Absent	20 (66.7%)
Walking	
Good	7 (23.3%)
With walking device	1 (3.3%)
With third-person aid	2 (6.7%)
Absent	20 (66.7%)
Skin assessment	
Pressure ulcers	4 (13.3%)

Discussion

This study provides insight into an understudied population of tracheostomized patients who are admitted to an SNF. The 30 units that responded to the online questionnaire had a total bed capacity of 983 patients (53 short-term, 263 medium-term, and 667 long-term). As of June 2017, a total of 2428 beds were available at SNFs in the north of Portugal.[10] Thus, the response rate was 40.1%.

In our sample, 33 patients needed tracheostomy ventilation, which corresponds to a prevalence of 3.36%. All of them were admitted to long-term units. The clinical spectrum included patients with stroke, cancer, acute respiratory distress syndrome, spinal cord injury, neuromuscular diseases, cerebral palsy, and cardiac failure.

In 2001, data from the Eurovent survey indicated the existence of 18 patients who underwent tracheostomy ventilation, indicating a prevalence of 0.17:100,000 in Portugal.[11] Another survey conducted by Portuguese home care companies identified a total of 84 patients with tracheostomy ventilation as of November 2018. There were 50 patients located in the north of Portugal. Only 14 patients were institutionalized, of which 7 were adults. The most common reason for tracheostomy was neuromuscular diseases.[12] In our sample, the most common indication for tracheostomy was acute respiratory failure. Our study included a smaller percentage of neuromuscular patients, which was possibly a result of this population receiving care at home instead of being institutionalized.

Furthermore, we found a higher number of patients who required tracheostomy ventilation (33 patients compared to 7 in the previous study). Only one patient used mechanical in-exsufflation, and another one had ventilator dependency. The remaining 28 patients probably would not be included in the Portuguese home care companies' survey because they did not have any equipment. Therefore, tracheostomized patients at SNFs constituted an understudied population.

Decannulation is a complex and multidisciplinary process, and there is no standard protocol. Patients' ability

to tolerate tube occlusion, their level of consciousness, the effectiveness of cough to manage secretions, and protected airways are factors to consider in determining whether to perform decannulation.[6,7] We concluded that only a few patients were undergoing tracheostomy capping. Moreover, SNFs in our study were understaffed and provided less rehabilitation therapy.

In some countries, specialized weaning units have been established to manage stable patients who have prolonged MV via artificial airways. These units provide proper rehabilitation equipment with a strong focus on ventilator weaning due to higher levels of expertise.[2,4,8] Some studies have described that these specialized facilities can have higher rates of weaning success with lower rates of complications and mortality.[13] This population could benefit from hospital discharge to such units.

This study had some limitations, such as a small sample size and a lack of clinical information in patient records (especially during ICU stays, which may influence the weaning process, or anthropometrics data). Also, we did not have information about health status of the other non tracheostomized patients admitted to the SNFs.

Conclusions

Prolonged MV is an important and complex issue that requires appropriate attention and support. This study provided useful information to improve the understanding of the current situation of tracheostomized patients who are admitted to SNFs in the north of Portugal. Despite the lower response rate, which may have induced bias, the results revealed a significant prevalence of institutionalized patients requiring tracheostomy ventilation. These facilities hardly provide the necessary care to perform decannulation safely and effectively due to understaffing and a lack of technical equipment.

The significant number of patients in this situation makes it important to identify reasons for keeping these subjects in SNFs. Further studies with larger populations are needed to better characterize this population and improve the planning and management of healthcare resources. There is increasing evidence that coordinated multidisciplinary teams can favorably influence the weaning process and the quality of care of tracheostomized patients. When patients cannot be fully weaned after the critical illness is resolved, there is often no place for them to receive the appropriate care. Alternative places should be considered, such as specialized weaning facilities with multidisciplinary teams that have knowledge in this area.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. Mayo Clin Proc. 2017;92:1382–400.
2. Lone N, Walsh TS. Prolonged mechanical ventilation in critically ill patients: epidemiology, outcomes and modelling the potential cost consequences of establishing a regional weaning unit. Crit Care. 2011;15:R102.
3. King AC. Long-term home mechanical ventilation in the United States. Respir Care. 2012;57:921–30.
4. Navalesi P, Frigerio P, Patzlaff A, Häußermann S, Henseke P, Kubitschek M. Prolonged weaning: from the intensive care unit to home. Rev Port Pneumol. 2014;20:264–72.
5. Bonvento B, Wallace S, Lynch J, Coe B, McGrath BA. Role of the multidisciplinary team in the care of the tracheostomy patient. J Multidiscip Healthc. 2017;10:391–8.
6. Marchese S, Corrado A, Scala R, Corrao S, Ambrosino N, Galavotti V, et al. Tracheostomy in patients with long-term mechanical ventilation: a survey. Respir Med. 2010;104:749–53.
7. Vaz IM, Maia M, Melo AMC, Rocha A. Desmame ventilatório difícil – o papel da Medicina Física e de Reabilitação. Acta Med Port. 2011;24:299–308.
8. Ambrosino N. Prolonged mechanical ventilation: new facilities and new models of care. Rev Port Pneumol. 2012;18:211–3.
9. Herer B. Outcomes of tracheostomized subjects undergoing prolonged mechanical ventilation in an intermediate-care facility. Respir Care. 2018;63:282–8.
10. Monitorização da Rede Nacional de Cuidados Continuados Integrados (RNCCI). 1° Semestre; 2017. Available from: http://www.acss.min-saude.pt/wp-content/uploads/2016/07/Relatorio_Monitorizacao_RNCCI_1_Semestre-2017.pdf [accessed 04.01.19].
11. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005;25:1025–31.
12. Winck JC. Long-term tracheostomy ventilation in Portugal: survey based on home care providers. Pulmonology. 2019, http://dx.doi.org/10.1016/j.pulmoe.2019.01.006.
13. Hannan LM, Tan S, Hopkinson K, Marchingo E, Rautela L, Detering K, et al. Inpatient and long-term outcomes of individuals admitted for weaning from mechanical ventilation at a specialized ventilation weaning unit. Respirology. 2013;18:154–60.

Pulmonol. 2020;**26(2)**:95–100

PULMONOLOGY

www.journalpulmonology.org

REVIEW

''Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art.''

Alexandru Corlateanu[a,*], Yamely Mendez[b], Yafeng Wang[c], Ricardo de Jesus Avendaño Garnica[d], Victor Botnaru[a], Nikolaos Siafakas[e]

[a] *Department of Respiratory Medicine, State University of Medicine and Pharmacy N̈icolae Testemitanu,̧ Chisinau, Moldova*
[b] *Research Physician at Faculty of Medicine ''Dr. Alberto Romo Caballero'', Universidad Autonoma de Tamaulipas. Research Assistant II at Baylor College of Medicine, Houston, Texas. USA*
[c] *Department of Epidemiology and Biostatistics, School of Health Sciences, Wuhan University, 185 Donghu Road, Wuchang District, Wuhan 430071, China*
[d] *Benemerita Universidad Autonoma de Puebla, Mexico*
[e] *Professor of Thoracic Medicine, Department of Thoracic Medicine, University General Hospital, Heraklion, Greece*

Received 22 October 2019; accepted 28 October 2019

KEYWORDS
COPD;
Phenotyping;
Emphysema;
Bronchitis;
Asthma;
Lung

Abstract Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous and multisystemic disease with progressive increasing morbidity and mortality. COPD is now widely accepted as a heterogeneous condition with multiple phenotypes and endotypes. This review will discuss the old and new concepts for the different types of COPD phenotypes, as well as the inclusion of them in current guidelines. Phenotypical approach to COPD is having huge impact on everyday practice and changed nonpharmacological and pharmacological management of COPD in last decade. However, phenotypical approach is small step to precision medicine in COPD management in the absence of big, specific and well-designed COPD trials with exact identification of phenotypes for more personalization of the treatment of COPD.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, Chronic Obstructive Pulmonary Disease; ATS, American Thoracic Society; FEV1, Forced expiratory volume in the first secon; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoint; FEV1, Forced Expiratory Volume in one secon; FVC, Forced Vital Capacity; NICE, British National Institute for Health and Clinical Excellence; LLN, Lower Limit of Normality; WHO, World Health Organization.

* Corresponding author at: University of Medicine and Pharmacy N̈icolae Testemitanu,̧ Stefan cel Mare street 165, 2004 Chisinau, Moldova.
E-mail addresses: alexandru_corlateanu@yahoo.com (A. Corlateanu), wonyhfon@whu.edu.cn (Y. Wang), ricardoag92@yahoo.com.mx (R.d.J.A. Garnica).

https://doi.org/10.1016/j.pulmoe.2019.10.006

Introduction

The most recent update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined the concept of Chronic Obstructive Pulmonary Disease (COPD) as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and or alveolar abnormalities, usually produced by major exposure to harmful particles or fumes.[1] It is a leading cause of morbimortality worldwide that is substantially increasing.[2]

In more recent years, the term phenotype has been introduced to help clinicians in the identification of the different types of COPD subgroups. The definition for ''phenotype'' is considered as ''the physical appearance or biochemical characteristic as a result of an interaction between the genotype and environment''. Moreover, the definition clearly states that a phenotype has to be a subgroup with a great impact in the prognosis (symptoms, exacerbations, response to therapy, rate of disease progression, or death).[3]

The first to have the idea of conceptualizing the different types of phenotypes was Snider, in 1989. With a nonproportional Venn diagram, the classic 3 subgroups of COPD were introduced: chronic bronchitis, emphysema, and asthma in three overlapping circles. Those subsets of patients were known to continuously have airway obstruction.[4] That concept was included in the 1995 American Thoracic Society (ATS) COPD guidelines.[5]

In the years after that concept was proposed, several studies have shown that the overlap is undoubtedly significant, and the knowledge of the pathogenesis has evolved over time, as well as the clinical characteristics. This overlap can be challenging for some clinicians because of the imprecision of the concepts and the different recommendations for the management from current respiratory guidelines.[6] Thus, the heterogeneity of these conditions led to the importance of phenotyping even though the patients share some features of two or even three of these conditions. Some clinicians may benefit from this classification to predict the outcome and set a specific patient-therapy.[7]

But from these phenotypes, the one that is likely to be considered as an entity on its own, or even as a separate syndrome is asthma. Some hypotheses divide asthma into more specific syndromes with distinct ''endotypes''. An endotype is proposed to be a subtype of a condition defined by a different pathophysiological mechanism.[8] This was proposed after some characteristics of asthma were not always present in large cohorts of patients, such as recurring symptoms, airflow obstruction, bronchial hyperreactivity and underlying inflammatory response.[9] Lötvall et al., proposed rules for defining the asthma endotypes after selecting 7 parameters such as clinical characteristics, biomarkers, lung physiology, genetics, histopathology, epidemiology, and treatment response. That resulted in 6 different phenotypes and 5 separate endotypes and the ideal approach for these patients should be endotype-specific.[10]

Another classic phenotype is emphysema, which is a significant component of COPD and the extent increases with increasing the severity of airflow limitation, making that subgroup a very stable phenotype. The same concept can be stated with chronic bronchitis, which is been associated with excess forced expiratory volume in the first second (FEV1) and is observed predominantly in young adults.[11] One clinical feature of the different types of phenotypes is the frequency and severity of exacerbations. Several clinical trials have demonstrated that only a small number of patients with COPD experienced exacerbations. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study which included 2138 patients established that a patient who suffered 2 or more exacerbations per year was classified with a stable phenotype. The exacerbations were defined as events that led a care provider to prescribe antibiotics or corticosteroids, as well as hospitalization. The exacerbation frequency was followed over a period of 3 years.[12] This has a great impact in the COPD prognosis because exacerbations are linked to a bad prognosis and an excess FEV1 decline.

Table 1 Classification of COPD phenotypes.

Widely accepted COPD phenotypes	Emerging COPD phenotypes
Chronic Bronchitic	Pulmonary cachexia phenotype
Emphysematous	Overlap COPD and bronchiectasis
Asthma-COPD-Overlap	Upper lobe-predominant Emphysema Phenotype
Frequent exacerbator	The fast decliner phenotype
Rare exacerbator	The comorbidities or systemic phenotype
	α1-Antitrypsin Deficiency
	No smoking COPD

The purpose of this article is to review the old and new concepts for the different types of COPD phenotypes, as well as the inclusion of them in current guidelines (Table 1).

Old and new phenotypes

Old classifications of phenotypes were A (Patients with chronic bronchitis, inflammatory phenotype, frequent exacerbator, systemic manifestations and with co-morbidities) and B (Patients with emphysema, pronounced lung hyperinflation and without frequent exacerbations). But the reality is that many more phenotypes are likely to exist, and all of them have become almost synonymous with a clinical subgroup, leading to limited alternatives for the pharmacological treatment. It is important to mention that although a reduction of the ratio of FEV1 to forced vital capacity (FVC) has been adopted as an unquestionable sign of airflow obstruction, there is no consensus of cut-off achievement to separate healthy patients from obstructive patients. This will make any definition of phenotype that has been described after a prospective analysis to be somehow inconsistent, especially when a based fixed FEV1/FVC < 0.70 ratio was not used. This fixed ratio has been included in GOLD and also by the British National Institute for Health and Clinical Excellence (NICE) and the Canadian Thoracic Society. But this does not imply that the diagnosis with COPD using a fixed ratio is more accurate and confirmed than using the FEV1/FVC below the lower 5th percentile or lower limit of normality (LLN), which decreases with age.[13] Because this definition leaves a large proportion of subjects with physiological abnormalities that also manifest

respiratory symptoms but do not satisfy the COPD diagnostic criteria, the patients will need to be approached from multiple dimensions (clinical, physiological, imaging and endotyping).[14]

Vestbo et al. suggested in 2014 the following phenotypes: asthma, bronchial hyperresponsiveness, bronchodilator reversibility, emphysema, hyperinflation, cachexia, chronic bronchitis, frequent exacerbations, and systemic inflammation.[15] However, this classification has changed over the years since the original idea. Weatherall et al., used a cluster analysis to explore the clinical phenotypes in a community population with airways disease. That analysis included 175 subjects and 5 clinical phenotypes were identified: 1) severe and markedly variable airflow obstruction with features of atopic asthma, chronic bronchitis, and emphysema; 2) features of emphysema alone; 3) atopic asthma with eosinophilic airways inflammation, 4) mild airflow obstruction without other dominant phenotypic features and 5) chronic bronchitis in nonsmokers.[16] The concept of clinical phenotype in COPD emerged as those attributes of the disease alone or in combination that describe differences between individuals with COPD in relation to parameters that have significance (i.e. symptoms, exacerbations, treatment response, progression of the disease or death).[3] These findings are relevant in establishing the phenotype response to various pharmacological treatments and to providing the most appropriate treatment.[17] For example, phosphodiesterase-4 inhibitors (Roflumilast or cilomilast) are only used in patients with chronic bronchitis and they help them in improving the likelihood of exacerbations. On the other hand, patients with COPD-asthma overlap phenotype show an enhanced response to inhaled corticosteroids.[18,19]

The use of analytic approaches, like cluster analysis, has advanced the study of phenotypes. They facilitate the identification of unique groups of related variables in an attempt to recognize features that might relate to both underlying disease biologically and clinically significant outcomes. Those approaches usually resulted from the use of data obtained from large cohorts of well-characterized patients to identify their relation between clinical variables and outcomes.[20] One of those analyses was the ECLIPSE[12] which provided significant information about the susceptibility of certain patients to develop exacerbations. An additional study by the Phenotype and Course of COPD subclassified groups of COPD patients with exacerbations. In this last mentioned study, 342 subjects with COPD who were hospitalized with their first exacerbation, were identified as belonging to 3 distinct COPD groups: 1) ''severe respiratory COPD'' characterized by airflow limitation (mean FEV1, 38% of predicted value), 2) ''moderate respiratory COPD'' marked by milder degrees of airflow limitation (mean FEV1, 58% of predicted value), 3) ''systemic COPD'' with similar milder airflow limitation but with a greater proportion of comorbidities such as obesity, cardiovascular disease and diabetes mellitus.[21] But there are many other ways of classifying phenotypes, like radiologic data that could be associated with some clinical features of COPD phenotypes. The COPDGene study was a multicenter observational study designed to identify genetic factors with COPD. Subjects of that study underwent inspiratory, whole-lung volumetric multidetector computed tomography (CT)[22] with measurement of total lung emphysema percentage. Using the data of that trial, Han and collaborators were able to determine that both bronchial wall thickness and total lung emphysema percentage were predictive factor of COPD exacerbation frequency in a continuous way independently of severity airflow limitation.[23]

But then again these phenotypes always have a physiologic explanation, and the classic Fletcher-Peto curve published in 1976, has been used over time to define susceptibility phenotypes of patients with COPD based on the rate of lung function decrease; the relationship between the variables (FEV1, age, smoking history) is still not well understood. This is because they stated that as airflow worsens, the symptoms increase but this varies enormously among individual patients.[24] Some researchers have been studying these variables and their relationship using prospective studies. Nishimura et al did a 5-year prospective follow-up study of patients with COPD in Japan to identify variables that might influence the rate of COPD progression. They evaluated lung function and CT scan results at baseline and twice-yearly lung function and clinical outcomes over the follow-up period. It resulted in a cohort with 3 groups: 1) sustained lung function, 2) slow rate of lung function decrease [30 mL/year decrease in FEV1] and 3) rapid rate of lung function decrease [60 ml/year decrease in FEV1].[25] The patients with sustained lung function had less evidence of emphysema and a higher number of circulating eosinophils, in comparison with those rapid progressors who had the highest ratio of emphysema demonstrated on CT scans and a lowest transfer coefficient for carbon monoxide.

At the same time, circulating eosinophils will need to be evaluated to differentiate airway eosinophilia and airway hyperresponsiveness. A prospective clinical study made by Kume et al examined the prevalence of airway eosinophilia and airway responsiveness in COPD patients who have neither symptoms nor past medical history of asthma and also explored the association of these pathophysiological features of asthma in the management for COPD. This was done by sputum qualitative and quantitative analysis in patients with COPD GOLD stage 1-3. Sputum eosinophils were observed in 65 subjects of 129 (50.4%) using qualitative analysis. Airway hyperresponsiveness was developed in 46.9% of these subjects, and the exacerbations were more frequently in lower-grade airway eosinophilia without ciclesonide than higher-grade airway eosinophilia with ciclesonide. These entities are characteristic features of asthma, but they may develop in the subject of patients with COPD who do not present any symptoms related to asthma or a previous diagnosis of asthma.[26]

Another characteristic of asthma is wheezing, and not all the COPD patients presented with wheezing and this could be another clinical phenotype that would help differentiate subgroups. The Taiwan Obstructive Lung Disease study was a retrospective, multicenter research study which assessed medical records from patients with COPD over 40 years, between November 2012 and August 2013. Here patients with asthma were excluded, and demographic data, lung function, symptom scores and frequency of acute exacerbations were recorded and analyzed. Also, they evaluated the differences between patients with and without wheezing. From 1096 patients with COPD, only 424 (38.7%) had wheezing phenotype, and from this group they had more acute

exacerbations within the past year analyzed than the non-wheezing group. The postbronchodilator FEV1 was lower in wheezing patients ($p < 0.001$) associating these patients with a worse COPD phenotype in comparison to those without that symptom.[27]

More important when trying to classify a patient into a phenotype, is to consider the tobacco smoke exposure history and the use of cigarettes. Even though smoking is a major risk factor for COPD, more than ¼ of COPD patients are non-smokers. A Korean cohort study made by Ji et al.[28] near a cement plant, observed smokers and non-smokers by a cutoff of a 5 pack-year smoking history. The non-smoker (n = 49) group resulted in younger patients with a superior BMI vs. the smoker group (n = 11) ($p < 0.05$). The smokers group had more emphysema than non-smokers but with a borderline statistical significance ($p = 0.051$). In this study the tobacco smoke exposure was highly associated with an emphysema phenotype, while exposure to biomass (i.e. cement) exhibited less emphysema and more air trapping and more structural lung changes on volumetric CT scans (Table 2).

A similar retrospective study was done in Spain by Golpe et al.,[29] where he observed 499 patients diagnosed with COPD by smoking or biomass exposure. Here 122 were classified into biomass exposure subgroup and 377 to the tobacco exposure. Male gender was higher in the tobacco group (92.1%) and there was more frequency of emphysema among the tobacco users. Prevalence of chronic bronchitis and exacerbations, comorbidities and hospital admission rate were equal between both groups. Similar results were found in a cross-sectional study where women exposed to biomass smoke, never-smokers and former smokers were observed in a COPD clinic in Mexico City, Mexico. In this study, women in the tobacco group had more significantly marked emphysema than in the biomass group. And in the biomass group these women had more air trapping than the tobacco group.[30] This study complemented the existing information about the significant differences in the clinical presentation of this phenotype, the pulmonary function test and CT finding between biomass group (such as wood, charcoal, grass or crop smoke) and tobacco smoke-related COPD. A revision by Torres-Duque et al.[31,32] reinforces the fact that wood smoke is a completely different phenotype.

The World Health Organization (WHO) estimates that biomass smoke exposure, or household air pollution, is responsible for 4.3 million deaths annually globally, with particular attention to South East Asian and Western Pacific regions. And even though biomass exposure and tobacco exposure are both associated with similar reductions in post-bronchodilator airflow obstruction, biomass exposure shows greater reduction in mid-expiratory flow and less pronounced markers of emphysema like air trapping. Moreover, it is documented that in biomass smoke exposure there is thickening of the basement membrane and lymphocytic predominance in a bronchoalveolar lavage fluid and some visualization of bronchial anthracofibrosis.[33]

However, in the above-mentioned study, there was a mixed COPD-asthma phenotype which was more prevalent in the biomass exposure subgroup.[31] And in more recent years, it has increased attention to the developement of this new COPD-asthma syndrome/phenotype that combined can affect a total of more than 60 million patients globally[34] and which is why the NOVELTY[35] study was originated in 2016. This trial is planned to end in 2021, and it is a global, prospective observational 3-year study enrolling ĩ2000 patients over 12 years of age from primary and specialist clinical practices in 19 countries (ClinicalTrials.gov identifier: NCT02760329). The primary objective of this study is to describe patient characteristics, treatment designs and disease burden over time, as well as to identify phenotypes and molecular endotypes that are associated with differential aftermaths throughout the time patients have suspected or even diagnosed asthma and COPD. The countries participating in this project are Argentina, Australia, Brazil, Canada, China, Colombia, Denmark, France, Germany, Italy, Japan, Mexico, the Netherlands, Norway,

Table 2 Definitions of widely accepted and emerging COPD phenotypes.

Widely accepted COPD phenotypes	
COPD phenotype	Definition
Chronic Bronchitic	The presence of productive cough more than 3 months per year in two or more consecutive years
Emphysematous	Presence of emphysema confirmed on imaging
Asthma-COPD-Overlap	Persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD (typically is asthmatic smoker)
Frequent exacerbator	Presence of frequent exacerbations (two or more per year)
Rare exacerbator	Presence of rare exacerbations (no or just one exacerbation)
Emerging COPD phenotypes	
COPD phenotype	Definition
Pulmonary cachexia phenotype	Body Mass Index lower than 21 kg/m2
Overlap COPD and bronchiectasis	HRCT confirmation of bronchiectasis and definite COPD diagnosis
Upper lobe-predominant emphysema phenotype	CT findings consistent of predominant upper lobe emphysema
The fast decliner phenotype	Rapid decline of lung function
The comorbidities or systemic phenotype	High comorbidities burden, predominantly cardiovascular and metabolic
α1-antitrypsin deficiency	Genetic condition cused by deficiency of α1-Antitrypsin
No smoking COPD	Induced by biomass exposure

South Korea, Spain, Sweden, UK and USA. The results of this study will enable accurate patient classification according to the clinical outcomes and the biomarker profiles, and consequentially support the development of advanced personalized therapies.

In spite of this, these studies were often performed in unselected populations of COPD and it is possible that different results could have been detected in selected subpopulations. As a consequence, there is a real need for larger studies to identify variables other than lung function to improve the risk assessment in patients with COPD.[18,36] This will benefit the clinicians for a development of COPD management guidelines.

Phenotyping and current COPD guidelines

The first Spanish COPD guidelines (GesEPOC) were developed in 2012 and it was one of the very early attempts to introduce the phenotypical approach into clinical practice.[37]

In 2016 a detailed analysis of national COPD guidelines across Europe and Russia was published.[38] This demonstrated high variability across national guidelines according to the detection of COPD phenotypes, determined probably by the different time of publishing of COPD guidelines. The classic COPD phenotypes of chronic bronchitis and emphysema were recognised in guidelines from the Czech Republic, England and Wales, Poland, Russia, Spain and Sweden (bronchitic only).

In the 2019 GOLD guidelines management of stable COPD was redefined: groups A, B, C, D are now used just for informing the initial treatment only.[1] Regarding follow-up, two outcomes are proposed: dyspnoea and exacerbations, with different individualized treatment algorithms. Blood eosinophil count is introduced as a biomarker for the likelihood to treatment with an inhaled corticosteroids.

The GOLD guidelines help the clinicians in the diagnosis and treatment of COPD. However, COPD is a very complex disease with a high index of morbimortality. Efforts to identify subgroups or phenotypes have been a challenge that has evolved with time. Siafakas et al recommend some modes of treatments by phenotyping the patient before starting therapy, but also noticed the lack of strong cluster studies.[39] As the medicine and technology advance, ongoing research highlights such biomarkers, have been incorporated into clinical guidelines, as the basis of clinical phenotypes.

Impact of phenotyping in the management of COPD

Phenotypical approach to COPD is having huge impact on everyday practice and haschanged nonpharmacological and pharmacological management of COPD in last decade.

In recent years some common reasons for the multiple failures of drug development in COPD have been described and analyzed, including inadequate target engagement of the drug, poor patient selection and use of clinical endpoints that are insensitive or inaccurate for detecting appropriate treatment responses.[40,41] It was shown that use of biomarkers for COPD phenotype patients and selecting only those who are likely to experience benefit from the drug dramatically increases the probability of success of novel drugs in phase IIa trials from Õ9% (pre-biomarker implementation) to 82% (with biomarker implementation).[40,41] Probably this combined complex approach with application of COPD phenotypes and new biomarkers will revolutionize COPD management in next years.

Conclusions

Phenotypical approach to COPD is having huge impact on everyday practice and has changed nonpharmacological and pharmacological management of COPD in last decade. However, phenotypical approach is small step towards precision medicine in COPD management in the absence of big, specific and well-designed COPD trials with exact identification of phenotypes for more personalization of the treatment of COPD.

Author contributions

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

Conflict-of-interest statement

No potential conflicts of interest. No financial support.

Acknowledgements

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.2019.10.006.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2019. Available from: http://www.goldcopd.org/. [September 2019].
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2095–128.
3. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes. Am J Respir Crit Care Med. 2010;182(5):598–604.
4. Snider GL. Chronic obstructive pulmonary disease: a definition and implications of structural determinants of airflow obstruction for epidemiology. Am Rev Respir Dis. 1989;140(3_pt_2):S3–8.
5. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. CHEST. 2003;124(2):474–81.

6. Celli B, Snider G, Heffner J, Tiep B, Ziment I, Make B, et al. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1995;152.
7. Speizer FE, Ware JH. Exploring different phenotypes of COPD. N Engl J Med. 2015;373(2):185–6.
8. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. The Lancet. 2008;372(9643):1107–19.
9. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol. 2004;113(1):101–8.
10. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011;127(2):355–60.
11. Chetta A, Olivieri D. The COPD Assessment Test in the evaluation of chronic obstructive pulmonary disease exacerbations. Expert Rev Respir Med. 2012;6(4):373–5.
12. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2010;363(12):1128–38.
13. Brusasco V. Spirometric definition of COPD: exercise in futility or factual debate? Thorax. 2012;67(7):569–70.
14. Segal LN, Martinez FJ. Chronic obstructive pulmonary disease subpopulations and phenotyping. J Allergy Clin Immunol. 2018;141(6):1961–71.
15. Vestbo J. COPD: definition and phenotypes. Clin Chest Med. 2014;35(1):1–6.
16. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J. 2009;34(4):812–8.
17. Miravitlles M, Soler-Cataluña JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J. 2013;41(6):1252–6.
18. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;(9).
19. de Oca MM, Halbert RJ, Lopez MV, Perez-Padilla R, Tálamo C, Moreno D, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. Eur Respir J. 2012;40(1):28–36.
20. Carolan BJ, Sutherland ER. Clinical phenotypes of chronic obstructive pulmonary disease and asthma: Recent advances. J Allergy Clin Immunol. 2013;131(3):627–34.
21. Garcia-Aymerich J, Gómez FP, Benet M, Farrero E, Basagaña X, Gayete À, et al. Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. Thorax. 2011;66(5):430–7.
22. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, et al. Genetic Epidemiology of COPD (COPDGene) Study Design. COPD. 2011;7(1):32–43.
23. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, et al. Chronic Obstructive Pulmonary Disease Exacerbations in the COPDGene Study: Associated Radiologic Phenotypes. Radiology. 2011;261(1):274–82.
24. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645–8.
25. Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, et al. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185(1):44–52.
26. Kume H, Hojo M, Hashimoto N. Eosinophil Inflammation and Hyperresponsiveness in the Airways as Phenotypes of COPD, and Usefulness of Inhaled Glucocorticosteroids. Front Pharmacol. 2019;10:765-.
27. Huang W-C, Tsai Y-H, Wei Y-F, Kuo P-H, Tao C-W, Cheng S-L, et al. Wheezing, a significant clinical phenotype of COPD: experience from the Taiwan Obstructive Lung Disease Study. Int J Chron Obstruct Pulmon Dis. 2015;10:2121–6.
28. Ji W, Lim MN, Bak SH, Hong S-H, Han S-S, Lee S-J, et al. Differences in chronic obstructive pulmonary disease phenotypes between non-smokers and smokers. Clin Respir J. 2018;12(2):666–73.
29. Golpe R, Suárez-Valor M, Martín-Robles I, Sanjuán-López P, Cano-Jiménez E, Castro-Añón O, et al. Mortality in COPD patients according to clinical phenotypes. Int J Chron Obstruct Pulmon Dis. 2018;13:1433–9.
30. Camp PG, Ramirez-Venegas A, Sansores RH, Alva LF, McDougall JE, Sin DD, et al. COPD phenotypes in biomass smoke- versus tobacco smoke-exposed Mexican women. Eur Respir J. 2014;43(3):725–34.
31. González-García M, Torres-Duque C. Wood smoke COPD: a new description of a COPD phenotype? Eur Respir J. 2014;44(1):261–2.
32. Torres-Duque CA, García-Rodriguez MC, González-García M. Is Chronic Obstructive Pulmonary Disease Caused by Wood Smoke a Different Phenotype or a Different Entity? Archivos de Bronconeumología (English Edition). 2016;52(8):425–31 [10.1016/j.arbr.2016.06.026].
33. Perret JL, Abramson MJ. Biomass smoke COPD: A phenotype or a different disease? Respirology. 2018;23(2):124–5.
34. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2013;2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163–96.
35. Reddel HK, Gerhardsson de Verdier M, Agustí A, Anderson G, Beasley R, Bel EH, et al. Prospective observational study in patients with obstructive lung disease: NOVELTY design. ERJ Open Res. 2019;5(1):00036–2018.
36. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Mathioudakis GA, Calverley PMA. COPD Phenotypes and Biomarkers: Introducing Personalised Medicine. Curr Respir Med Rev. 2013;9(6):372–8.
37. Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Guía Española de la EPOC (GesEPOC). Tratamiento farmacológico de la EPOC estable. Archivos de Bronconeumología. 2012;48(7):247–57.
38. Miravitlles M, Vogelmeier C, Roche N, Halpin D, Cardoso J, Chuchalin AG, et al. A review of national guidelines for management of COPD in Europe. Eur Respir J. 2016;47(2):625–37.
39. Siafakas N, Corlateanu A, Fouka E. Phenotyping Before Starting Treatment in COPD? COPD. 2017;14(3):367–74.
40. Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, et al. Lessons learned from the fate of AstraZenecas drug pipeline: a five-dimensional framework. Nat Rev Drug Discov. 2014;13:419.
41. Leung JM, Obeidat ME, Sadatsafavi M, Sin DD. Introduction to precision medicine in COPD. Eur Respir J. 2019;53(4):1802460.

Pulmonol. 2020;**26(2)**:101–103

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Janus-faced amiodarone-induced pneumopathy

To the Editor,

Several forms of pulmonary disease can occur among patients treated with amiodarone (usually delivered as an antiarrhythmic drug). Computed tomography findings indicative of amiodarone-induced lung disease include high-attenuation parenchymal-pleural lesions and nonspecific pulmonary infiltrates. Only a few cases in the literature have described the occurrence of amiodarone-induced pulmonary disease as pulmonary nodules. The authors describe a patient showing bilateral, peripheral, predominantly basal ground-glass and reticular opacities consistent with a non-specific interstitial pneumonia (NSIP) radiological pattern. This was followed by the occurrence of two nodules that progressively decreased in size after oral steroids had been given and therefore they were interpreted as an unusual manifestation of amiodarone-related pulmonary toxicity (APT).

A 79-year-old man, a non-smoker and who had a history of atrial fibrillation, was treated with amiodarone 400 mg daily for 3 years. During the last 2 months of treatment, he was presented with exertional dyspnea and dry cough. Respiratory function tests revealed a restrictive ventilatory pattern with a moderate reduction in carbon dioxide lung diffusion (DLCO) (14.3 mL/min/mmHg, 55% of predicted value). Chest computed tomography (CT) showed bilateral, peripheral, predominantly basal ground-glass and reticular opacities consistent with a NSIP radiological pattern (Fig. 1, panels A and B). The bronchoalveolar lavage showed a significant amount of foamy macrophages. Transbronchial lung biopsy of the right lower lobe was performed and the histological examination revealed the presence of septal widening with type II pneumocytes hyperplasia, areas of organized interstitial fibrosis with sporadic fibrinous exudates, fibroblasts and collagen deposition next to aggregates of inflammatory cells and considerable amount of foamy histiocytes. These findings were consistent with a diagnosis of APT (Fig. 1, panels C and D). Other etiologies of interstitial lung disease (ILD) were carefully ruled out. Amiodarone was suspended while prednisone 40 mg daily and oral anticoagulants were given, with rapid clinical and functional recovery. At 40 days, ground-glass and reticular opacities had almost completely resolved on CT scan while two soft-tissue nodules of 25 and 11 mm, respectively, were identified in the right costophrenic sulcus (Fig. 2, panels A and B). Both lesions presented elevated density on CT scan images with Hounsfield Unit (HU) values ranging from 46 to 50. The patient underwent a new bronchoscopy with bronchoalveolar lavage of the right lower lobe, but microbiological and cytological investigations were unremarkable. A tuberculin skin test and blood serological markers for autoimmunity, inflammatory and infectious disease were also performed with negative results. Moreover a supplemental investigation was conducted excluding the onset of new drug treatment, trauma or exposure to environmental agents. Given their rapid onset, the elevated HU values and the exclusion of other coherent etiologies, the nodules were interpreted as an unusual subacute manifestation of APT. As physical insult to pulmonary parenchyma is known to increase susceptibility to toxicity even if low dose amiodarone treatment is used,[1] surgical lung biopsy was not performed and radiological follow-up was started. At 18 months, follow-up CT showed a considerable reduction in the size of both lung nodules (Fig. 2, panels C and D) and the clinical condition of the patient was unremarkable.

Amiodarone, one of the most widely used antiarrhythmic agents, is known to cause adverse lung effects in approximately 5% of treated patients.[2] Several risk factors for the development of lung complications have been identified: the pre-existence of lung disease and/or respiratory failure requiring high oxygen mixtures, lower respiratory tract infections, older age, treatment duration and a history of cardiothoracic surgery.[3] Since the patient had been taking amiodarone for 2 years before developing respiratory symptoms, a dose accumulation effect might be suspected in this case.[2,3] For most patients, the diagnosis of amiodarone-induced pneumopathy relies on imaging.[4] According to available literature, lung involvement presents a wide range of possible manifestations: from asymptomatic lipoid pneumonia, which is usually named the 'amiodarone effect', to the 'amiodarone toxicity' spectrum, which embraces different clinical entities such as eosinophilic pneumonia, chronic organizing pneumonia (COP), acute fibrinous organizing pneumonia (AFOP), nonspecific interstitial pneumonia (NSIP)-like and idiopathic pulmonary fibrosis (IPF)-like interstitial pneumonia, desquamative interstitial pneumonia (DIP), acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage and, more rarely, isolated or multiple nodular or mass-like lesions.[2,4,5] Amiodarone-related pulmonary nodules usually generate high attenuation areas on CT scans due to the incorporation of iodine-rich amiodarone into type II pneumocytes.[6] In this form, the radiological presentation of drug-induced toxicity might mimic malignant neoplasms.[7] In most cases, patients respond well to the withdrawal of amiodarone with the addition of corticosteroid treatment, with

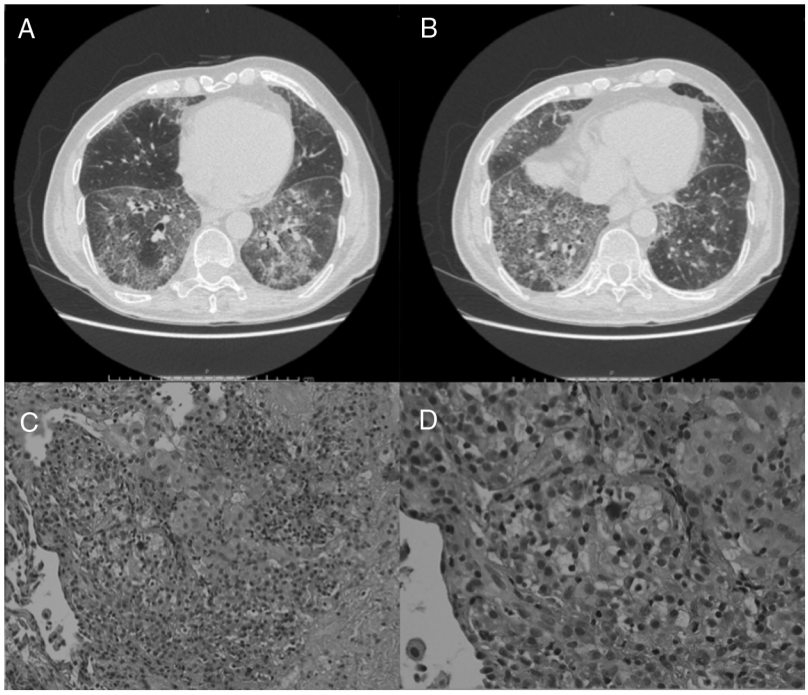

Figure 1 (Panels A and B) CT scan images showing predominantly basal, bilateral, peripheral ground-glass opacities with associated reticular abnormalities consistent with a non-specific interstitial pneumonia (NSIP) radiological pattern. (Panels C and D) Histological appearance at different magnifications of transbronchial biopsies showing areas of organized fibrosis with fibrinous exudates and significant amount of inflammatory cells and with no evidence of malignant cells.

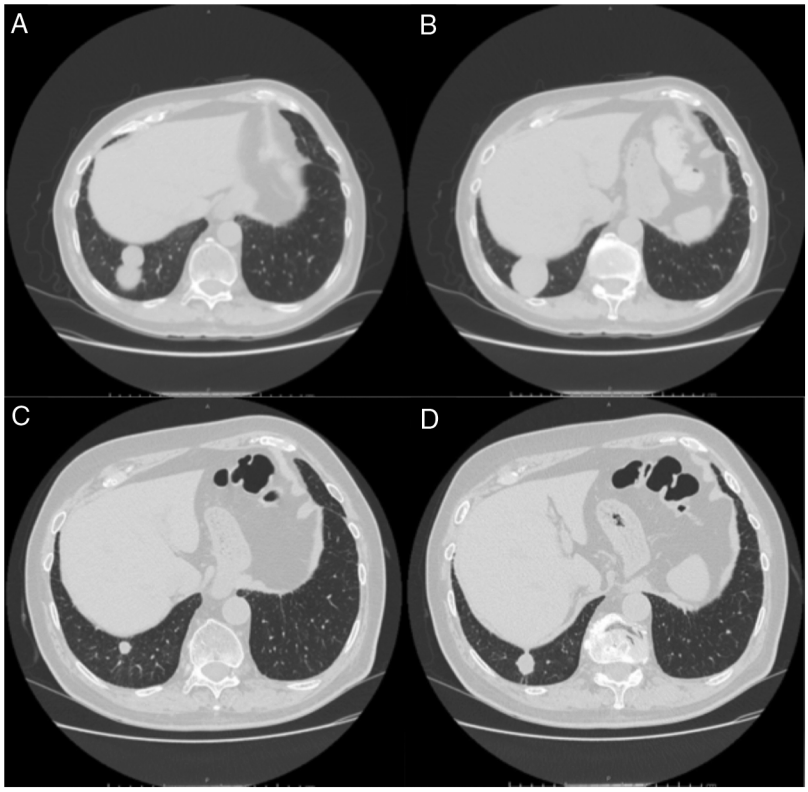

Figure 2 (Panels A and B) CT scan images showing the resolution of the ground-glass and reticular opacities after amiodarone withdrawal and the onset of two large nodules of 25 mm and 11 mm, respectively, which ensued in the right costophrenic sulcus. (Panels C and D) Follow-up CT images showing a substantial reduction in size of the right costophrenic nodules 18 months after amiodarone withdrawal.

symptoms and radiological abnormalities resolving within several months due to the long half-life of the amiodarone metabolites.[8]

The peculiarity of our case was the sequential occurrence of reversible interstitial NSIP-like lung abnormalities followed by nodular high-density opacities. Moreover, the onset of lung nodules occurred after the withdrawal of amiodarone and once corticosteroid treatment had been started. Several hypotheses on the late-onset of lung nodules could be made. A late-onset direct toxic injury to lung parenchyma and/or a slow immunologic reaction should not be excluded.[2] However given that the nodules were located in the same lobe where the first biopsy had been performed, a possible increase in lung susceptibility to amiodarone toxic effect after physical insult might be suspected.[1]

To the best of our knowledge, this is the first case of a biphasic manifestation of amiodarone-related lung toxicity with large reversible nodules following interstitial abnormalities. The broad imaging manifestations of APT may account for some temporal heterogeneity.

Consent to publish data

Informed consent to publish data was obtained by the patient.

Funding

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

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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

References

1. Schwaiblmair M, Berghaus T, Haeckel T, et al. Amiodarone-induced pulmonary toxicity: an under-recognized and severe adverse effect? Clin Res Cardiol Off J German Cardiac Soc. 2010;99:693–700.
2. Papiris SA, Triantafillidou C, Kolilekas L, Markoulaki D, Manali ED. Amiodarone: review of pulmonary effects and toxicity. Drug Saf. 2010;33(7):539–58.
3. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. Br J Clin Pharmacol. 2008;66(1):82–7.
4. Ott MC, Khoor A, Leventhal JP, et al. Pulmonary toxicity in patients receiving low-dose amiodarone. Chest. 2003;123:646–51.
5. Van Mieghem W, Coolen L, Malysse I, et al. Amiodarone and the development of ARDS after lung surgery. Chest. 1994;105:1642–5.
6. Chouri N, Langin T, Lantuejoul S, et al. Pulmonary nodules with the CT halo sign. Respiration. 2002;69:103.
7. Piccione W Jr, Faber LP, Rosenberg MS. Amiodarone-induced pulmonary mass. Ann Thorac Surg. 1989;47:918–9.
8. Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. Clin Pharmacol Ther. 1995;58:692–8.

S. Cerri[a], R. Tonelli[a], P. Faverio[b], N. Sverzellati[c], E. Clini[a,*], F. Luppi[b]

[a] *Center for Rare Lung Diseases, Respiratory Disease Unit, University Hospital of Modena and University of Modena and Reggio Emilia, Modena, Italy*
[b] *Respiratory Unit, University of Milano Bicocca, S. Gerardo Hospital, Monza, Italy*
[c] *Section of Radiology, Unit of Surgical Sciences, Department of Medicine and Surgery (DiMeC), University of Parma, Parma, Italy*

[*] Corresponding author.
E-mail address: enrico.clini@unimore.it (E. Clini).
Available online 3 August 2019

https://doi.org/10.1016/j.pulmoe.2019.07.003
2531-0437/

Pulmonary cavities—The diagnostic's challenge

Dear Editor,

A pulmonary cavity is defined as a gas-filled space within a zone of pulmonary consolidation or within a mass or nodule, often seen as a lucency or low-attenuation area.[1] Cavities are present in a wide variety of processes, such as lung cancer, autoimmune diseases, infections, congenital malformations and trauma. A chest X-ray and computed tomography (CT) are the radiographic means most often used to assist diagnosis.[1,2]

Traumatic pulmonary pseudocysts (TPP) are uncommon cavitary lesions developed as consequence of blunt thoracic trauma. They are more frequent in children and young adults.[3,4]

A 16-year-old female, equestrian practitioner went to the emergency room because of right chest trauma caused by two horse kicks. She denied any symptoms other than pain. Physical examination showed two bruises and severe pain on palpation of right costal grid and sternum, without other changes.

Chest and ribs X-rays were normal. Thoracic CT performed on the same day as the horse kicks, demonstrated two cavities, one in the lower lobe of the right lung with air-fluid level and 70 mm diameter (Fig. 1) and other in the

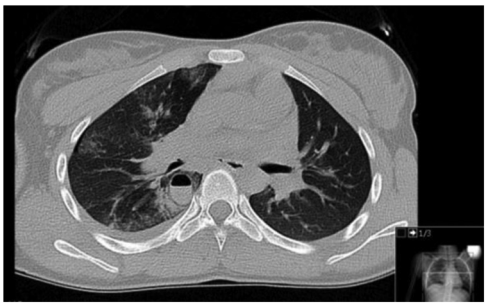

Figure 1 Thoracic CT demonstrating a cavitary lesion ($70 \times 28\,mm^2$) in the lower lobe of the right lung with air-fluid level and several diffuse alveolar consolidations.

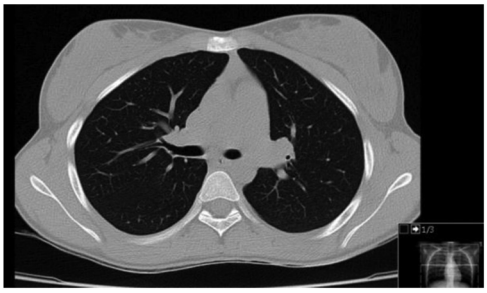

Figure 2 Thoracic CT performed 3 months later demonstrating complete resolution of the pulmonary lesions.

medial segment of the middle lobe with 15 mm diameter, without broken ribs.

White blood cell count revealed leucocytosis (18.200 cells/μL) with neutrophilia (15.900 cells/μL). Mantoux test, Mycoplasma and HIV serology were negative; immunoglobulin A, G and M and complement C3 and C4 were normal; blood culture and aerobic, anaerobic and fungal cultures of bronchoalveolar lavage were negative.

She completed empirical treatment with ampicillin and clindamycin for 10 days. Thoracic pain improved gradually and she remained asymptomatic and was discharged to adolescent consultation. Follow-up CT performed 3 months after the episode demonstrated a complete resolution of the pulmonary changes seen in the previous study (Fig. 2).

TPP is an uncommon cavitary lesion lacking an epithelial lining or bronchial wall elements, which develops within the pulmonary parenchyma after blunt chest trauma. Such pseudocysts can occur at any age but they are most frequent (80–85%) in children and young adults.[3,4]

The mechanism by which this injury occurs is not known exactly, but it is believed that younger people have a more elastic and pliable chest wall, which permits greater transmission of kinetic energy to the intrathoracic structures such as pulmonary parenchyma.[3–5] The rapid compression and decompression lacerates alveoli and interstitium. Retraction of the elastic tissue of the lung results in small cavities filled with air and/or fluid. Cavities tends to grow until the pressure of the adjacent parenchyma equals the intracavitary pressure.[3–6] Another proposed mechanism is that the closure of the glottis or bronchial obstruction, at the moment of trauma, makes it difficult for the air to escape in the compressed segment and the lacerated parenchyma forms a cavity.[4,6]

Most TTP appear in the first 12 h after the trauma. However, they can occur immediately or within a few days of the injury.[3,6] The patient may be asymptomatic or manifest subtle or nonspecifc symptoms such as cough, chest pain, hemoptysis and dyspnea. Occasionally, they also present with mild fever and leucocytosis.[4,6,7]

TTP can be detected on chest X-ray, but CT is better for identification.[4,6] Their sizes range from 2 to 14 cm in diameter and they can be spherical or oval, single or multiple, unilateral or bilateral. They may be observed on the site of injury or on the other side and the majority are found in lower lobes.[3–6]

The differential diagnosis is extensive and includes infections such as tuberculosis, mycosis, lung abscess and pneumatocele, autoimmune diseases, lung cancer, bronchogenic cysts and adenomatoid cystic malformation. The history of chest trauma and the presence of a contusion at the site of the impact usually help the diagnosis, but if the cavitary lesion does not decrease with time, other etiology must be considered.[5,6]

TPP are benign lesions and the treatment is generally conservative. Spontaneous resolution usually occurs within 6 weeks after the trauma in adults and 3–4 months in children.[5,6] The use of empirical antibiotic therapy should not be a routine and is only warranted by persistent fever, leucocytosis, radiographic modifications, or other signs of infection.[4,7]

In conclusion, the differential diagnosis of pulmonary cavities includes a wide variety of diseases. The authors emphasize the importance of considering pulmonary pseudocysts when cavities appear in the context of a high energy trauma in patients without comorbidities, and no prior systemic symptoms. In this case, the temporal relationship with chest trauma and the fact that the whole study was normal corroborated the diagnosis of traumatic pulmonary pseudo cysts, a rare condition found in less than 3% of cases.[4,7]

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Gadkowski LB, Stout JE. Cavitary pulmonary disease. Clin Microbiol Rev. 2008;21(2):305–33.
2. Parkar AP, Kandiah P. Differential diagnosis of cavitary lung lesions. J Belg Soc Radiol. 2016;100(1):1–8.
3. Celik B, Basoglu A. Post-traumatic pulmonary pseudocyst: a rare complication of blunt chest trauma. Thorac Cardiovasc Surg. 2006;54(6):433–5.
4. Yazkan R, Ozpolat B, Sahinalp S. Diagnosis and management of post-traumatic pulmonary pseudocyst. Respir Care. 2009;54(4):538–41.
5. Chon SH, Lee CB, Kim H, et al. Diagnosis and prognosis of traumatic pulmonary pseudocysts: a review of 12 cases. Eur J Cardiothorac Surg. 2006;29(5):819–23.
6. Gupta N, George J, Gupta RC, Dixit R. Traumatic pulmonay pseudocyst. Int j Crt llln lnj Sci. 2013;3(2):155–8.

7. Melloni G, Cremona G, Ciriaco P, Pansera M, Carretta A, Negri G, et al. Diagnosis and treatment of traumatic pulmonary pseudocysts. J Trauma. 2003;54(4):737–43.

Francisca Martins*, Ariana Teles, Idalina Maciel, Hugo Rodrigues

Pediatric Department, Unidade Local de Saúde do Alto Minho, Viana do Castelo, Portugal

* Corresponding author at: Estrada de Santa Luzia, 4904-858 Viana do Castelo, Portugal.

E-mail address: franciscamartins8@hotmail.com (F. Martins).

12 March 2019

https://doi.org/10.1016/j.pulmoe.2019.07.011
2531-0437/

Autonomy and dyspnea in palliative care: A case report

Introduction

Dyspnea is a complex and subjective experience, its intensity is wholly determined by the patient's sensation and how it is perceived depends on previous beliefs, emotions, values and experiences.[1,2] Several measures are employed to alleviate dyspnea, which must be acceptable to the patient. Thus, therapeutic adherence is promoted, and a good symptomatic control is achieved, as illustrated in the present case.

Case report

M.S., female, 61 years old, divorced, retired, with asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) diagnosed four years ago, and still worsening, currently under noninvasive ventilation (NIV) and long-term oxygen therapy (LTOT). She has a history of hypertensive heart disease and anxiety disorder. She is an ex-smoker (40 Units Year Package).

She was followed in outpatients clinics in General and Family Medicine and Pulmonology, suffering from irreversible respiratory insufficiency, which was potentially difficult to control due to therapeutic failure. She had had multiple admissions to acute hospitals due to the exacerbation of her pathology, ending up being referred to and admitted into a Palliative Care Unit (PCU) for symptomatic control of dyspnea and fatigue. On admission she presented with a grade 4 dyspnea (Modified Dyspnea Scale Medical Research Council) and a performance status of 4 (Eastern Cooperative Oncology Group). Her Palliative Performance Scale was 50–60%. She was prescribed montelukast 10 mg id, aminophylline 225 mg bid, tiotropium bromide 1.25 mcg 2 id inhalations, fluticasone/salmeterol 250/25 mcg 2 bid inhalations, salbutamol 100 mcg PRN inhalations, lisinopril 5 mg id, omeprazole 20 mg id, and hydroxyzine 25 mg bid.

After her admission to the PCU, therapeutic adjustments were made according to her symptoms. Prolonged-release morphine was prescribed (10 mg bid) after proper titration with immediate-release morphine (5 mg PRN), butylscopolamine 20 mg tid, prednisolone 10 mg id and laxatives (macrogol 13.7 g bid and sennosides 7.5 mg bid). Due to the patient's refusal to keep on LTOT and NIV, even after multiple adjustments, they were progressively reduced and suspended; yet symptomatic control was not compromised. Likewise, due to the patient's non-compliance with inhalation therapy, without the symptomatic relief expected, and considering her wishes, it was suspended. She used a hand fan, but because there was an air conditioner unit in the room, she preferred to turn it on. Pulse oximetry, when measured, was more than 90%. A physical rehabilitation plan was implemented with an adaptative training program.

Because she complained of pruritus, an opioid-related side-effect, morphine dose was initially reduced, and an opioid rotation to tapentadol was done.

At follow up evaluation after three weeks, through daily clinical evaluation, symptoms have been well controlled: dyspnea and fatigue are mild (self-assessment). She is fully motivated to her rehabilitation plan and shows good compliance with it.

Currently her regular medications are: escitalopram 10 mg id, pantoprazole 20 mg id, aminophylline 225 mg bid, lorazepam 1 mg id, tapentadol 50 mg bid, prednisolone 5 mg id and bisacodyl 5 mg id.

Discussion

Patients diagnosed with ACOS are over 40 years old (15–55% of them are over 50 years old) and experience frequent exacerbations, showing a quick decline in lung function and high mortality.[3]

Mrs MS frequent exacerbations and worsening of her clinical condition were considered to be due to lack of motivation to adhering to the therapeutic regimen and other inherent factors. In fact, perhaps Mrs MS did not understand the therapeutic plan, or the medications she was prescribed were not adjusted to her needs. Moreover, a lack of an effective doctor–patience communication may have led to non-compliance and therapeutic failure.

The principle of autonomy respects the ability of an individual to self-determination, allowing or enabling patients to make their own decisions about any medical interventions.[4] Consequently, the doctor-patient relationship has moved from a paternalistic and disease-centered model to a person-centered care model. Informed consent is essential to the latter process and the patient has the right to refuse any intervention that is proposed.[5]

In Portugal, according to Decree-Law no. 25/2012 (July 16th), a legally aged and capable person, who is not prohibited or disabled by psychiatric abnormality, can declare and specify the type(s) of healthcare he/she wishes to receive, or not, in case of – for any reason – he/she finds

him/herself unable to express his/her preferences, personally and autonomously, in the form of advance directives, namely in the form of a living will. This document has to record provisions relating to healthcare for serious or irreversible illnesses at an advanced stage, including appropriate symptomatic therapy.

Mrs MS had neither interest nor the will to keep to a therapeutic plan that included inhalers, masks or any other of the respiratory accessories that were proposed, which is the reason why she did not comply with them at all. With Mrs MS preferences and in her best interest in mind, pharmacological adjustments were made to her plan of care, leading to good symptomatic control and excellent therapeutic adherence.

In palliative care (PC), in advanced respiratory diseases, symptomatic relief of dyspnea is of capital importance. Pharmacologic palliation of dyspnea involves the use of opioids, oxygen, and/or benzodiazepines.[6] Systematic opioids therapy are the mainstay of palliative pharmacologic management of severe dyspnea and their effectiveness has been demonstrated in numerous clinical trials.[6–8] However, a recent systematic review suggests that some of the evidence that shows benefit from their use is of low quality.[9] In many studies that have used opioids for the relief of dyspnea, it has been stated that the initial dose for a specific patient is to be defined according to the intensity of dyspnea reported, preferably through self-assessment; and after the titration phase the dose should be readjusted.[10,11] The ideal therapeutic dose is the minimum dose that promotes, from the patient's perspective, both good symptomatic control and tolerable/acceptable side effects. The opioid prescription should happen according to the patient's functional status and in agreement with previous opioid use.

Often, anxiety is a factor to take in consideration, as it contributes to symptomatic exacerbations, therefore therapy should be adjusted accordingly. The effect of morphine and its analogs is amplified when used in combination with benzodiazepines.[1,12]

Mrs MS's weaning from oxygen therapy may be considered controversial – since this therapy is often used in the end-of-life as a first-line strategy in the management of dyspnea. However, Mrs MS had demanded the weaning to proceed. The indications for oxygen therapy in advanced disease are partial, with no evidence of improved survival.[1]

The use of a low-dose systemic corticosteroid treatment has been advocated. In PC, the prescription of corticosteroids in a low-dose/short duration scheme has been described, without great evidence about its benefits. Corticosteroids are pluripotent drugs that can be used in pain control (as adjuvant analgesics), nausea/vomit control, appetite and lethargy management (syndrome of anorexia-cachexia), etc.[13]

NVI is an extremely important measure, usually well accepted by patients, unlike what happened to this patient probably due to her anxiety.[14] It would be considered effective if it improves dyspnea without causing other troubling consequences.[15] Other non-pharmacological interventions are also used to control dyspnea, such as appropriate room environment, adequate body positioning, breathing, physiotherapy techniques and acupuncture.[16,17] Several studies have demonstrated inadequate symptom management in patients with advanced respiratory disease, the discomfort of physicians in prescribing opioids is one of the contributors to this.[18] Although there is a growing awareness about the need for PC in end-stage non-neoplastic respiratory diseases, there are some accessibility and clinical issues that prevent patients being referred to PC services. Sometimes, physicians' reluctance and/or difficulties to define ''a palliative care status'' may contribute to that.[19]

The present case reflects: (a) the respect for each patient's preferences and autonomy in clinical practice; (b) the prescription of less common treatments for dyspnea control, such as opioids, corticosteroids and benzodiazepines in PC; (c) the importance of shared decision-making in clinical management of patients with advanced disease.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Feio M. Dispneia. In: Barbosa A, Pina PR, Tavares F, Neto IG, editors. Manual de Cuidados Paliativos. 3rd ed. Lisboa: Faculdade de Medicina Lisboa; 2016. p. 219–29.
2. Pisani L, Hill NS, Pacilli AMG, Polastri M, Nava S. Management of dyspnea in the terminally ill. Chest. 2018;154:925–34.
3. GINA/GOLD. Diagnosis of diseases of chronic airflow limitation: asthma, COPD and asthma-COPD overlap syndrome (ACOS). A joint project of GINA and GOLD; 2015. Available from: https://goldcopd.org/asthma-copd-asthma-copd-overlap-syndrome/ [accessed 31.01.19] [online publication].
4. Ascensão JO. Estudos de Direito de Bioética, vol. III. Coimbra: Almedina; 2009. p. 151–5.
5. Pereira AGD. O Consentimento Informado na Relação Medico-Paciente: estudo de direito civil. Coimbra: Coimbra Editora; 2004. p. 33–5.
6. Kamal AH, Maguire JM, Wheeler JL, Currow DC, Abernethy AP. Dyspnea review for the palliative care professional: treatment goals and therapeutic options. J Palliat Med. 2012;15:106–14, http://dx.doi.org/10.1089/jpm.2011.0110.
7. Jennings AL, Davies AN, Higgins JP, Broadley K. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database System Rev. 2001. CD002006.
8. Lanken PN, Terry PB, Horace M, et al. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illness. Am J Respir Crit Care Med. 2008;177:912–27.
9. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev. 2016;3:CD011008.
10. Clemens KE, et al. Is there a higher risk of respiratory depression in opioid-naïve palliative care patients during symptomatic therapy of dyspnea with strong opioids? J Palliat Med. 2008;11.
11. Viola R, et al. The management of dyspnea in cancer patients: a systematic review. Support Care Cancer. 2008;16: 329–37.
12. Clemens KE, Klaschik E. Dyspnoea associated with anxiety – symptomatic therapy with opioids in combination with lorazepam and its effect on ventilation in palliative care patients. Support Care Cancer. 2011;19:2027–33.
13. Denton A, Shaw J. Corticosteroid prescribing in palliative care settings: a retrospective analysis in New Zealand. BMC Pall Care. 2014;13:7, http://dx.doi.org/10.1186/1472-684X-13-7.

14. Nava S, Ferrer M, Esquinas A, Scala R, Groff P, Cosentini R, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncol. 2013;14:219–27.
15. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
16. Bausewein C, Booth S, Bysels M, Higginson I. Nonpharmacologic interventions for breathlessness in advanced stages of malignant and nonmalignant diseases. Cochrane Database System Rev. 2008;2:CD005623.
17. A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD): the COPD-Acupuncture Trial (CAT). |Chronic Obstructive Pulmonary Disease|JAMA Internal Medicine|JAMA Network; 2019. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1151703 [cited 29.04.19] [Internet].
18. Young J, Donahue M, Farquhar M, Simpson C, Rocker G. Using opioids to treat dyspnea in advanced COPD. Can Fam Physician. 2012;58:e401–7.
19. Pamplona P, Bárbara C. Cuidados Paliativos e Insuficiência Respiratória Crónica. In: Barbosa A, Pina PR, Tavares F, Neto IG, editors. Manual de Cuidados Paliativos. 3rd ed. Lisboa: Faculdade de Medicina Lisboa; 2016. p. 447–65.

M. Martins[a,*], E. Campôa[b], M. Ferreira[c], P. Reis-Pina[c,d]

[a] *Unidade de Saúde Familiar do Dafundo, Lisboa, Portugal*
[b] *Serviço de Oncologia Médica, Centro Hospitalar Universitário do Algarve, Faro, Portugal*
[c] *Unidade de Cuidados Paliativos São Bento Menni, Casa de Saúde da Idanha, Belas, Sintra, Portugal*
[d] *Centro de Bioética, Faculdade de Medicina, Universidade de Lisboa, Portugal*

Corresponding author.
E-mail address: monicateixeiramartins@gmail.com (M. Martins).

27 February 2019 2 May 2019

https://doi.org/10.1016/j.pulmoe.2019.05.005
2531-0437/

Catathrenia resolved with the lowest CPAP pressure settings

Introduction

Catathrenia is a rare sleep disorder first described by Roeck et al.[1] Originally classified as a parasomnia, it is currently included within the group of respiratory sleep disorders. Its incidence, prevalence, and physiopathology are unknown, and its onset is more frequent in adolescents and young adults of average weight. Bed partners are the ones who commonly report strange sounds while breathing during sleep, as affected individuals are unaware of their problem.

Catathrenia usually occurs during REM sleep, though it may be also present in other stages. A catathenia event is characterized by a repeated groaning or moaning sound during prolonged expiration preceded by a deep inhalation and accompanied by a breathing pattern marked by bradypnea of variable duration. Its clinical relevance remains uncertain; catathrenia is considered a self-limited benign condition causing no negative effects beyond significant social nuisance. Although still debated, a significant proportion of patients with catathrenia do report disrupted sleep and some sleepiness or tiredness as in our current case.[2] There is little documented experience in treating the condition, but some studies have shown resolution of events with continuous positive airway pressure (CPAP). Here we describe a patient with substantial clinical repercussions due to sleep fragmentation, responding favorably to CPAP without a need for treatment at high-pressure levels.

Abbreviations: CPAP, continuous positive airway pressure; SDB, sleep-disordered breathing; REM, rapid eye movement sleep; PSG, polysomnography; AHI, Apnea/hypopnea index; RDI, respiratory disturbance index.

Case report

A 22-year-old average-weight (BMI 24) woman with no relevant medical history who did not smoke or drink complained of nocturnal groaning and arousals due to the noise which caused sleep fragmentation, low quality of sleep, daytime tiredness, and headache predominantly in the morning hours. An examination was performed on the patient, including neurologic and otolaryngology assessment and pulmonary function examination, revealing no pathological findings that could explain the clinical symptoms.

A polysomnography (PSG) was carried out showing apnea/hypopnea index (AHI) of 4.8e/h, desaturation index of 0e/h, and respiratory disturbance index (RDI) of 14e/h. The PSG revealed 18 cathathrenia events, most of which occurred from REM sleep. These events were characterized by prolonged expiration with acute sound during bradypnea without oxygen desaturation, lack of effort in the chest and abdomen, and sleep fragmentation related to the electroencephalographic arousals secondary to these events (Fig. 1). The results of the study confirmed the diagnosis of catathrenia. Based on the clinical impact, CPAP treatment was administered at a pressure of 4 cmH_2O.

To confirm treatment results, a respiratory polygraphy test with a microphone was performed on 2 consecutive nights. We conducted a baseline polygraphy test (Fig. 2) which detected catathrenia noise with the typical signs in flow/effort bands without desaturation. In the following polygraphy with a low CPAP pressure setting (4 cmH_2O) minimal residual events were observed.

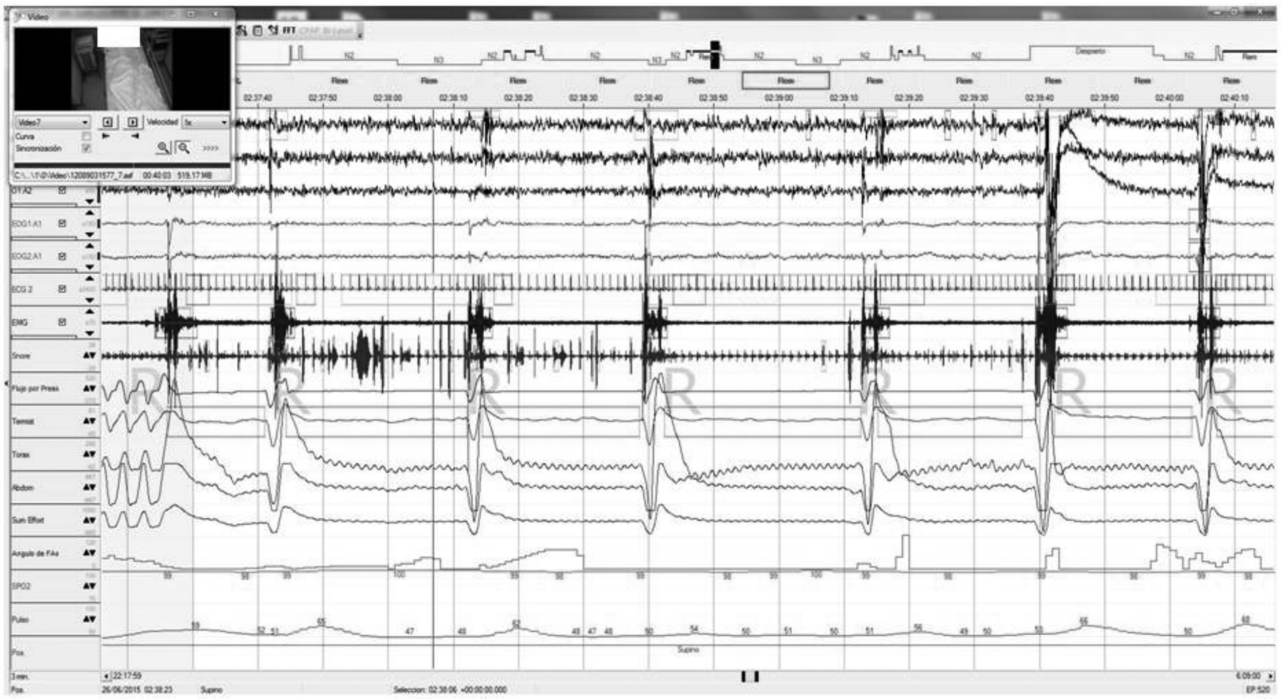

Figure 1 Baseline polysomnography: This figure evidences nocturnal characteristic bradypnea without effort in the chest/abdomen or oxygen desaturation. Associated electroencephalographic (EEG) arousals during stage REM. EEG channels (from top to bottom): C4/A1, C3/A2, O2/A1, EOG1/A1, EOG2/A1, ECG, EMG, snore, flow, thermistor, chest band, abdominal band, sum of band readings, phase angle, oxygen saturation, heart rate and position.

Clinical response to CPAP was excellent; she has improved her daytime sleepiness and remains free of symptoms showing a good compliance after 24 months.

Discussion

We present the case of a patient with substantial clinical repercussions stemming from catathrenia. A sleep study confirmed sleep fragmentation secondary to catathrenia events (deep inspiration followed by a prolonged expiration associated with a groaning, followed by a brief expiration and deep inspiration) as evidenced by the fact that each event was associated with an electroencephalographic (EEG) arousal. For the sake of description, we used the methods appearing in the case series of Guilleminault et al. in which only those sleep epochs with 2 or more events were included in the analysis.[3]

Our patient had 18 epochs with at least 2 breaths marked by catathrenia, and another 7 breaths did not meet the aforementioned criteria. Although the total duration was short (9 min for the entire reading), these events involved marked sleep fragmentation and poor sleep quality. The respiratory events do not sufficiently explain the symptoms in this patient, as AHI and desaturation index were normal, and an RDI of 14 was only reached following flow limitation. Additional tests were carried out, including pulmonary function test and neurological and otolaryngology assessment; these did not evidence any type of anatomical or other abnormality such as those described by Zeliang et al.[4]

Given the clinical repercussions caused by the condition, a therapeutic test consisting of CPAP at a pressure of 4 cm H_2O was performed. Although substantially higher-pressures are recommended in the literature,[3,6] a substantial improvement was achieved in our patient. Guilleminault et al.[3] showed that their patient's groaning responded completely using CPAP (higher-pressure settings: 7–10 cmH_20). These pressures were pursued to eliminate flow limitation (abnormal RDI was present in these series of cases) but pleased to find the resolution of catathrenia events. In our case, a second sleep study was carried out to confirm response; in this case polygraphy was used, as in the report of Romigi et al.,[5] this procedure may be useful for screening and diagnosis of this pathology when there is high suspicion of catathrenia. The NOX-T3 sleep monitor, which is equipped with a directional microphone, was used for polygraphy studies. The test was performed on 2 consecutive nights in order to compare the first night (baseline) to the second, during which a low CPAP pressure setting was administered. The length of both studies was comparable.

A significant number of events secondary to catathrenia were observed on the first night, with each of these 38 events leading to body movements that can suggest arousals (no confirmation is available since we lack EEG in this test). AHI and RDI were slightly lower than the observed in the PSG (AHI 3e/h, RDI 12e/h). The following night with the lowest-pressure settings of CPAP we observed that almost all catathenia events disappeared; there was a substantial reduction in the number of events from 38 to 8 events with improvement in clinical presentation despite persistence of AHI of 2e/h and RDI of 9e/h. Treating catathrenia events associated with abnormal RDI usually leads to the increased pressures described by Guilleminault et al.[3] It remains con-

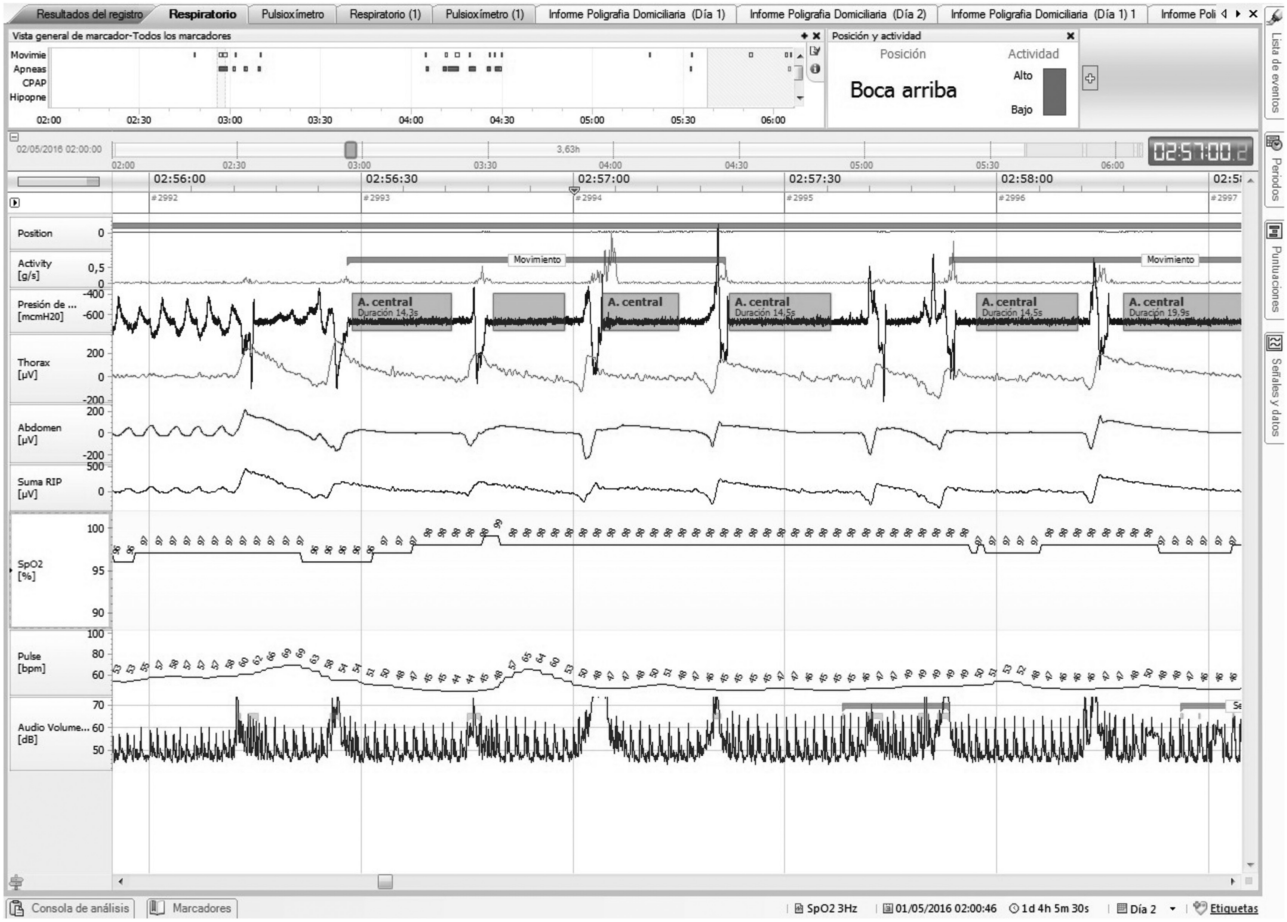

Figure 2 Baseline polygraphy: EEG channels (top to bottom): position, activity, flow, chest band, abdominal band, sum of band readings, oxygen saturation, heart rate, and microphone. There is noise all through the events (microphone channel). Following each event there is an increase in activity signal.

troversial if titrating CPAP to eliminate flow limitation may be associated with improved clinical outcomes compared to treating apneas or hypopneas.[7] We believe our patient, despite her young age, has remained compliant with CPAP for over two years due to the clinical benefit produced at the lowest pressure settings of CPAP. There are other studies were catathrenia was treated with selected soft tissue surgeries of the upper airway or with mandibular advancement device.[8]

In summary, catathrenia is an uncommon disorder characterized by a distinct breathing pattern in which CPAP treatment seems to be effective but its utility is limited by poor patients acceptability. Setting CPAP pressures to control cathatrenia events (leaving aside flow limitation) could be related to better CPAP compliance.

Author's contributions

TG and AC were responsible for the conception and design of the study, and wrote and edited the manuscript. MP-C, PR, MF-T and FE contributed to the drafting and revision of the manuscript. All authors read and approved the final manuscript.

Funding

This study was undertaken without funding.

Conflicts of interest

We wish to confirm that are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial manager and direct communications with the office). She is responsible for communicating with the other authors

about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept e-mail from ana.casal.mourino@sergas.es

We confirm that the manuscript is not published elsewhere, in any language, and is not under simultaneous consideration by any other journal. Signed by all authors as follows:

Teresa Gómez
Ana Casal
María del Pilar Carballosa De Miguel
Paula Rodríguez Rodríguez
María Fernanda Troncoso Acevedo
Farah Ezzine De Blas

References

1. De Roek J, Van hoof E, Cluydts R. Sleep related expiratory groaning. A case report. J Sleep Res. 1983;12:237.
2. Pevernagie DA, Boon PA, Mariman AN, Verhaeghen DB, Pauwels RA. Vocalization during episodes of prolonged expiration: a parasomnia related to REM sleep. Sleep Med. 2001;2(1):19–30.
3. Guilleminault Christian, Hagen Chad C, Khaja Aluddin M. Catathrenia: parasomnia or uncommon feature of sleep disordered breathing? Sleep Med. 2008;31(1):132–9.
4. Hao Zeliang, Xu Liyue, Zhang Jinjjing, XueliLan Xuemei Gao, Han Fang. Anatomical characteristics of catathrenia (nocturnal groaning) in upper airway and orofacial structures. Sleep Breath. 2016;20:103–11.
5. Romigi Andrea, Vitrani Giuseppe, D'Aniello Alfredo, Di Gennaro Giancarlo. Can nocturnal groaning be suspected by cardiorespiratory polygraphy? Sleep Med. 2014;15:1002–5.
6. Songu Murat, Yilmaz Hikmet, Yuceturk Ali Vefa, Gunhan Kivanc, Ince Aysun, Bayturan Ozgur. Effect of CPAP therapyoncatathrenia and OSA: a case report and review of the literatura. SleepBreath. 2008;12:401–5.
7. Arora Nevin, Meskill Gerad, Guilleminault Christian. The role of flow limitation as an important diagnostic tool and clinical finding in mild sleep-disordered breathing. Sleep Sci. 2015;8(3):134–42.
8. Drakatos Panagis, Marples Lucy, Muza Rexford, Higgins Sean, Gildeh Nadia, Macavei Raluca, Dongol Eptehal M, Nesbitt Alexander, Rosenzweig Ivana, Lyons Elaine, d'Ancona Grainne, Steier Joerg, Williams Adrian J, Kent Brian D, Leschziner Guy. NREM parasomnias: a treatment approach based upon a retrospective case series of 512 patients. Sleep Med. 2019;53:181–8.

Teresa Gómez[a,b], Ana Casal[c,*], María del Pilar Carballosa De Miguel[a], Paula Rodríguez Rodríguez[a], María Fernanda Troncoso Acevedo[a,b], Farah Ezzine De Blas[a]

[a] *Pneumology Department, Hospital Fundación Jiménez Díaz, Spain*
[b] *Respiratory research group CIBERES*
[c] *Pneumology Department, Hospital Clínico Universitario, Santiago de Compostela, Spain*

Corresponding author at: Pneumology Department, Hospital Clínico Universitario, Santiago de Compostela, Travesía da Choupana s/n, 15706 Santiago de Compostela, Spain.
E-mail addresses: tgomez.garcia@quironsalud.es (T. Gómez), ana.casal.mourino@sergas.es (A. Casal), maria.carballosa@quironsalud.es (M.d.P.C. De Miguel), paula.rrodriguez@quironsalud.es (P.R. Rodríguez), mftroncoso@quironsalud.es (M.F.T. Acevedo), FEzzine@quironsalud.es (F.E. De Blas).

1 April 2019 23 July 2019

https://doi.org/10.1016/j.pulmoe.2019.07.010
2531-0437/

Pulmonol. 2020;**26(2)**:111–113

PULMONOLOGY

www.journalpulmonology.org

CORRESPONDANCE

Community-based pulmonary rehabilitation during acute exacerbation of chronic obstructive pulmonary disease: Pilling up the evidence

To the Editor,

I read with interest the paper of Machado et al. regarding the effects of a community-based pulmonary rehabilitation program (PR) during acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD).[1] Pulmonary rehabilitation is a multicomponent regime known to improve exercise capacity, functional capacity and quality of life and reduce symptom burden and hospitalizations among COPD patients.[2] Current ERS/ATS statement recommends the implementation of a home-based PR program for exacerbated COPD patients who present at hospital; however the level of recommendation is moderate, since published data is currently limited.[3] Moreover, the optimal time point of initiation and the PR program that could provide the most benefit is still to be identified. The study of Machado et al.[1] offers further interesting information in this context. The severity of obstruction and its potential impact on the outcomes of the PR program would be an interesting addition to the study results. Although the study sample is rather small, so subject categorization according to the severity of the disease is probably not possible, it would be interesting to know whether the effect of this community-based PR program was similar among COPD patients with moderate, severe and very severe obstruction. Similarly, this data would be useful for exploring characteristics of drop-outs, since published data in PR studies indicate that those patients who drop out have more severe disease overall, than the ones who complete the intervention.[4]

The lack of characterization of the severity of COPD acute exacerbation (AECOPD) can be reported as a limitation of Machado et al. study.[1] According to Global Obstructive Lung Disease (GOLD), AECOPD is classified as mild when treated with extra short-acting bronchodilators, as moderate when treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids, while in severe AECOPD patient requires hospitalization or visits the emergency room.[5] Since participants in both groups (experimental and control) were identified by pulmonologists at hospital, one would expect that they suffered from severe or moderate-to-severe exacerbation. However, the data from the medication usage is rather contradictory; no extra bronchodilation was given to any of the patients, while the use of antibiotics and/or oral corticosteroids tend to differ between the groups. It is unlikely that the results of this study would have been different if medication usage was similar between the groups. Nevertheless, accurate characterization of the severity of AECOPD would offer valuable information as to who can receive a community-based PR program during exacerbation and who would benefit the most.

The authors have to be commended for offering a multidimensional program including psychoeducational and nutritional support, respiratory training, muscle strengthening and aerobic training, which they describe in detail. However, the exact point in time for starting PR has to be accurately defined. Published data indicate that PR outcomes differ when it is initiated early or late after AECOPD onset,[6] so this is an issue that has to be further addressed in detail.

In conclusion, a community-based multidimensional PR program seems to be safe and effective for COPD patients during acute exacerbation. More prospective, randomized trials are needed in order to define the optimal outpatient PR regimen and when it should be initiated, according both to the severity of COPD and the severity of acute exacerbation.

Conflict of interest

None.

Acknowledgments

No funding received.

References

1. Machado A, Oliveira A, Valente C, Burtin C, Marques A. Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease – A quasi-experimental pilot study. Pulmonology [in press] https://doi.org/10.1016/j.pulmoe.2019.05.004.
2. 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 Resp Crit Care. 2015;192:1373–86.
3. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;49(March (3)), pii: 1600791.
4. Boutou AK, Tanner RJ, Lord VM, Hogg L, Nolan J, Jefford H, et al. An evaluation of factors associated with completion and benefit from pulmonary rehabilitation in COPD. BMJ Open Respir Res. 2014;1(November (1)):e000051.
5. Global Initiative for Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of chronic

obstructive pulmonary disease. 2019 Report. Available at: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.6-FINAL-08Nov2018-wms.pdf.
6. Matsui H, Jo T, Fushimi K, Yasunaga H. Outcomes after early and delayed rehabilitation for exacerbation of chronic obstructive pulmonary disease: a nationwide retrospective cohort study in Japan. Respir Res. 2017;18:68.

Afroditi K. Boutou[1], Theodoros Kontakiotis[2]

[1] *Department of Respiratory Medicine, G. Papanikolaou Hospital, Thessaloniki, Greece Exohi, 57010 Thessaloniki, Greece*

[2] *Department of Respiratory Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece*
E-mail address: afboutou@yahoo.com (A.K. Boutou).

19 June 2019
Available online 25 September 2019

https://doi.org/10.1016/j.pulmoe.2019.07.005
2531-0437/

Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease - A quasi-experimental pilot study. Authors' reply

We are grateful to Dr. Boutou[1] for her reassuring letter about our manuscript entitled ''Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease – A quasi-experimental pilot study.''[2] The most appropriate time point to begin pulmonary rehabilitation during an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and who can benefit the most from this comprehensive intervention is indeed a similar ''Holy Grail'' on how to maintain the benefits after pulmonary rehabilitation.[3] It is worth noting that in the latest Cochrane review of Puhan and co-workers,[4] from the 20 studies included, 13 were conducted with inpatients,[5–17] although 80% of the AECOPD are managed on an outpatient basis,[18] when patients are integrated in the community. This relative lack of research exploring the benefits of pulmonary rehabilitation when patients are integrated into their daily routines and environment and supported by their loved ones, might be ''blurring'' our understanding of the role of pulmonary rehabilitation considering the whole picture of the AECOPD. Our pilot study contributed to clarify this role, by showing that pulmonary rehabilitation is a safe, feasible and effective intervention for these patients, however, more studies following robust methodologies are urgently needed.

Another important aspect that might contribute to misunderstanding the role of pulmonary rehabilitation during AECOPD is the healthcare context of each country. For example, in the letter of Dr. Boutou[1] her understanding was that because our patients were identified by pulmonologists at the hospital, patients would be suffering from severe or moderate-to-severe exacerbations. Yet, in our healthcare system, when an AECOPD occurs most patients go to the hospital to be assessed by a doctor and have their medication adjusted, and it does not necessarily mean that they are having a severe exacerbation. In fact, a wide variety in the severity of exacerbations will come up on a daily basis at the hospital, hence different medication usage. Most cases are sent to be managed on an outpatient basis and it was those patients that were recruited for our study. Although it is unlikely that different responses would have been obtained about the pulmonary rehabilitation based on different medication usage, which would have meant stratifying patients per exacerbation severity, it is important that future studies explain in a more detailed manner the healthcare context where recruitment occurs to avoid misinterpretations of the clinical profile of patients included in the studies.

We agree with Dr. Boutou[1] that timing is key to determining the success of an intervention. In our study, participants' first assessment was performed within 48 h of the diagnosis of AECOPD and the intervention started within 72 h. Our results further add to those of Matsui and colleagues showing that, for patients treated in the community, early interventions may result in improvements in muscle strength, impact of the disease and symptoms.[19]

In fact, in our study, an analysis per severity of airflow obstruction was not performed. Although lung function is an essential component of the diagnostic of COPD, no significant relationship between lung function and response to pulmonary rehabilitation has been found in patients with stable COPD.[20] Moreover, not all severely obstructed patients are highly symptomatic and limited in their daily living and some of those with mild obstruction are also known to experience high symptom burden and activities limitation.[21,22] It is therefore, unlikely that based on the restriction of the airflow obstruction differential responses would have been obtained.[22]

In conclusion, community-based pulmonary rehabilitation seems to benefit patients with AECOPD but further research on the multidimensional assessment of patients, identification of who can most benefit, time of initiation and best regimen following a person-centred approach[22] are areas that need future rigorous research.

Acknowledgements

This work was funded by Programa Operacional de Competitividade e Internacionalização – POCI, through Fundo Europeu de Desenvolvimento Regional - FEDER (POCI-01-0145-FEDER-007628; POCI-01-0145-FEDER-028806), Fundação para a Ciência e Tecnologia (PTDC/DTP-

PIC/2284/2014; PTDC/SAU-SER/28806/2017) and under the project UID/BIM/04501/2019).

References

1. Boutou AK, Kontakiotis T. Community-based pulmonary rehabilitation during acute exacerbation of chronic obstructive pulmonary disease: Pilling up the evidence; 2019, http://dx.doi.org/10.1016/j.pulmoe.2019.07.005.
2. Machado A, Oliveira A, Valente C, Burtin C, Marques A. Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease - A quasi-experimental pilot study. Pulmonology. 2019, http://dx.doi.org/10.1016/j.pulmoe.2019.05.004.
3. Rochester CL, Spruit MA. Maintaining the Benefits of Pulmonary Rehabilitation. The Holy Grail. Am J Resp Crit Care. 2017;195:548–51.
4. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;12:Cd005305.
5. Kirsten DK, Taube C, Lehnigk B, Jorres RA, Magnussen H. Exercise training improves recovery in patients with COPD after an acute exacerbation. Respir Med. 1998;92:1191–8.
6. Nava S. Rehabilitation of patients admitted to a respiratory intensive care unit. Arch Phys Med Rehab. 1998;79:849–54.
7. Behnke M, Jorres RA, Kirsten D, Magnussen H. Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. Monaldi Arch Chest Dis. 2003;59:44–51.
8. Carr SJ, Hill K, Brooks D, Goldstein RS. Pulmonary rehabilitation after acute exacerbation of chronic obstructive pulmonary disease in patients who previously completed a pulmonary rehabilitation program. J Cardiopul Rehabil. 2009;29:318–24.
9. Eaton T, Young P, Fergusson W, Moodie L, Zeng I, O'Kane F, et al. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. Respirology. 2009;14:230–8.
10. Troosters T, Probst VS, Crul T, Pitta F, Gayan-Ramirez G, Decramer M, et al. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. Am J Resp Crit Care. 2010;181:1072–7.
11. Tang CY, Blackstock FC, Clarence M, Taylor NF. Early rehabilitation exercise program for inpatients during an acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial. J Cardiopul Rehabil. 2012;32:163–9.
12. Borges RC, Carvalho CR. Impact of resistance training in chronic obstructive pulmonary disease patients during periods of acute exacerbation. Arch Phys Med Rehab. 2014;95:1638–45.
13. Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. BMJ. 2014;349:g4315.
14. Torres-Sánchez I, Valenza MC, Valenza-Demet G, Cabrera- Martos I, Flores-Barba MJ, Ruíz-Sáez A. Quality of life in hospitalized patients for exacerbation of COPD included in a physical therapy program. Chest. 2014;145:372A (3 ṀeetingAbstracts).
15. He M, Yu S, Wang L, Lv H, Qiu Z. Efficiency and safety of pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease. Med Sci Monit. 2015;21:806–12.
16. Liao LY, Chen KM, Chung WS, Chien JY. Efficacy of a respiratory rehabilitation exercise training package in hospitalized elderly patients with acute exacerbation of COPD: a randomized control trial. Int J Chron Obstruct Pulmon Dis. 2015;10:1703–9.
17. Torres-Sanchez I, Valenza MC, Saez-Roca G, Cabrera-Martos I, Lopez-Torres I, Rodriguez-Torres J. Results of a Multimodal Program During Hospitalization in Obese COPD Exacerbated Patients. COPD. 2016;13:19–25.
18. GOLD. Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2019 report. In: The Global Initiative for Chronic Obstructive Lung Disease; 2019. p. 1–155.
19. Matsui H, Jo T, Fushimi K, Yasunaga H. Outcomes after early and delayed rehabilitation for exacerbation of chronic obstructive pulmonary disease: a nationwide retrospective cohort study in Japan. Respir Res. 2017;18:68.
20. Augustin IML, Wouters EFM, Houben-Wilke S, Gaffron S, Janssen DJA, Franssen FME, et al. Comprehensive Lung Function Assessment Does not Allow to Infer Response to Pulmonary Rehabilitation in Patients with COPD. J Clin Med. 2018;8.
21. Annegarn J, Meijer K, Passos VL, Stute K, Wiechert J, Savelberg HH, et al. Problematic activities of daily life are weakly associated with clinical characteristics in COPD. J Am Med Dir Assoc. 2012;13:284–90.
22. Spruit MA, Augustin IM, Vanfleteren LE, Janssen DJ, Gaffron S, Pennings HJ, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. Eur Respir J. 2015;46:1625–35.

Ana Machado[a,b], Ana Oliveira[a,b], Carla Valente[c], Chris Burtin[d,e], Alda Marques[a,b,*]

[a] *Lab 3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences, University of Aveiro, Aveiro, Portugal*
[b] *Institute of Biomedicine (iBiMED), University of Aveiro, Aveiro, Portugal*
[c] *Pulmonology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal*
[d] *REVAL – Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium*
[e] *BIOMED – Biomedical Research Institute, Hasselt University, Hasselt, Belgium*

[*] Corresponding author at: Lab 3R – Respiratory Research and Rehabilitation Laboratory, School of Health Sciences and Institute of Biomedicine (iBiMED), University of Aveiro (ESSUA), Agras do Crasto - Campus Universitário de Santiago, Edifício 30, 3810-193 Aveiro, Portugal.

E-mail addresses: filipamachado@ua.pt (A. Machado), alao@ua.pt (A. Oliveira), carlavalente77@hotmail.com (C. Valente), chris.burtin@uhasselt.be (C. Burtin), amarques@ua.pt (A. Marques).

30 August 2019

https://doi.org/10.1016/j.pulmoe.2019.09.001
2531-0437/

Pulmonol. 2020;**26(2)**:114–115

PULMONOLOGY

www.journalpulmonology.org

BREAKING NEWS

And now for something completely different: from 2019-nCoV and COVID-19 to 2020-nMan

Infectious diseases have accompanied mankind since the beginning of humanity and have had a profound impact on the history and development of humanity and civilisation. This is natural if we are aware that microorganisms represent the majority of the biomass on planet Earth, and that there are more microorganisms, specifically bacteria, in the human body than there are cells. To be more precise, about 1012 human cells for every 1013 bacteria, as an adaptive advantage of the replication of bacteria that occurs every 20–40 min, as against tens of years in the human species.

Infectious diseases, in particular pandemics and local epidemics, have influenced the course of wars, all descendants, including those of rulers, and the fate of peoples and nations.[1] By way of example, we should remember the importance of malaria in the fall of the Roman Empire, the Black Death in the 14th century which killed nearly a third of the world's population, and the impact of the ''Spanish'' flu pandemic of 1918–19 in Portugal, which in a few months decimated 1% of the Portuguese population and reduced average life expectancy to 20 years and, more recently, smallpox, declared eradicated by the World Health Organization (WHO) in 1980 as a result of vaccination,[2] and with an estimated mortality in the 20th century of between 300 and 500 million people.[3]

In light of this impact, it is legitimate to consider infections one of the main modellers of mankind and of present and future generations, as well as generations of the descendants of survivors.

We have also been major challengers of infectious diseases in the 21st century. Most notably in 2009 and 2010, when the 2009 influenza pandemic caused by the A (H1N1) subtype strain occurred, which originated in Mexico, with a virulence rate of 5–10% of the world's population, and an estimated mortality of 300,000 people. In Portugal there were 124 deaths, with an average age of 47.6 years, corresponding to a crude death rate of 1.17 per 100,000 inhabitants.[4]

However, it is in the first decades of the 21st century when the number of outstanding cases corresponded entirely to Coronaviridae of the family Coronaviridae, from the Latin corona, given its crown shape under electronic microscope. These viruses belong to a large family of RNA viruses, with abundant expression in the animal kingdom, particularly bats, and also other mammals, birds and reptiles. The first outbreak of coronavirus disease was the result of a cross-species barrier jump, originating in bats, and probably the musk cat as a secondary host, which began on November 16, 2002 and was named SARS-CoV (Severe Acute Respiratory Syndrome - CoronaVirus) in Guangdong Province, of the People's Republic of China, and extended to 17 countries, including Canada, the United States of America (USA), Australia, Germany, France, Sweden, the United Kingdom and Spain. The WHO declared an end to the risk of new cases on 19 May 2004, with an estimated total of approximately 8096 cases and at least 774 deaths.[5]

A new outbreak occurred in 2012 in Saudi Arabia, subsequently named MERS-CoV Middle East Respiratory Syndrome-related CoronaVirus. This virus, also originating from bats, and using intermediate hosts, camels and dromedaries, had its greatest expression in the Middle East, and the risk of new cases is still not considered to be over. Up until June 2015, it is estimated to have affected approximately 2506 people, with 862 deaths, in about 26 countries, including the USA and several European Union countries.[6]

Finally, in December 2019 a new outbreak of coronavirus was detected in the city of Wuhan, Hubei Province, China, which was provisionally named 2019-nCoV (nCoV for new coronavirus). The first known fatal case was recorded on January 9, 2020, and on February 11, 2020, due to its similarity to the initial SARS-CoV the WHO named this new coronavirus SARS-CoV-2, and the disease, COVID-19 (COronaVIrus Disease-19).[7]

By 25 February 2020, the number of cases had exceeded 80,000 in 39 countries or special regions, with more than 2700 deaths.[8] Evidence of transmission chains in communities in other countries and continents outside China confirms the increased risk of a possible pandemic.

Through these three global outbreaks of coronavirus disease in the 21st century we have seen a marked improvement in diagnostic response, particularly in molecular

https://doi.org/10.1016/j.pulmoe.2020.02.010

biology and genome sequencing. Yet, unfortunately, this improvement in diagnosis has not translated equally into the development of targeted therapies and vaccines. Ideally, the development of vaccines against common segments of the coronavirus would bring greater scope in terms of preventing current and future outbreaks.

Finally, in an increasingly global world, these outbreaks greatly reinforce the perpetual and recurring challenge of infectious diseases in the history and lives of individuals and civilisations. If we cannot expect the behaviour of infectious agents to change, it is down to us to promote knowledge and expertise, individually and collectively. Only thus can we minimise the risks of exposure, ensure early detection and timely diagnosis, and adopt the most effective infection control, therapeutic and preventive measures. We must never lose the humility to learn from mistakes and bear in mind the fundamental role of social communication in safeguarding a transparent and coherent risk assessment and management strategy. In other words, we must learn how to evolve in the wake of these new Coronaviruses, the nCoVs, to make a sustained and responsible change in our behaviour and attitudes. New citizens, new mankind: 2020-nMan.

References

1. Fauci AS, Morens DM. The perpetual challenge of infectious diseases. N Engl J Med. 2012;366(February 2 (5)):454–61.
2. World Health Organization. Smallpox. https://www.who.int/csr/disease/smallpox/en/ (online access 25/02/2020).
3. Koplow David A. Smallpox: the fight to eradicate a global scourge. Berkeley: University of California Press; 2003.
4. Froes F, Diniz A, Falcão I, et al. Final report on the mortality from flu pandemic (H1N1) 2009 in Portugal (April 2009-August 2010). Rev Port Saúde Pública. 2014;32(1):55–60.
5. National Health Service (NHS). SARS (severe acute respiratory syndrome). https://www.nhs.uk/conditions/sars/ (online access 25/02/2020).
6. World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). https://www.who.int/emergencies/mers-cov/en/ (online access 25/02/2020).
7. World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (online access 25/02/2020).
8. Worldometer. COVID-19 Coronavirus Outbreak. https://www.worldometers.info/coronavirus/ (online access 25/02/2020).

F. Froes
ICU, Thorax Department, Lisboa, Portugal
E-mail address: filipe.froes@gmail.com

ClinicalKey®

CK

The ClinicalKey Mobile App is here!

Leverage insights for better patient outcomes anytime, anywhere with the ClinicalKey mobile app – available for both Apple® and Android™ devices.

ClinicalKey helps clinicians rapidly access evidence-based, peer reviewed information to improve speed to accurate diagnosis and treatment, with the goal of improving patient outcomes and lowering the high cost of care.

Start your ClinicalKey mobile experience today!

- Open the App Store on your mobile device
- Search for "ClinicalKey" and install at no charge
- Once in the app, two options will appear – Click on ClinicalKey
- Enter your ClinicalKey username and password used for remote access and start using the ClinicalKey App!

Your institution must subscribe to ClinicalKey in order for you to use the app.
To sign up for a free 30-day trial, visit clinicalkey.com.au/info

Lead with answers.

ELSEVIER