HIGHLIGHT

Bedside Lung Ultrasound

PROGRAME-SE

XVI CURSO NACIONAL DE ATUALIZAÇÃO EM PNEUMOLOGIA

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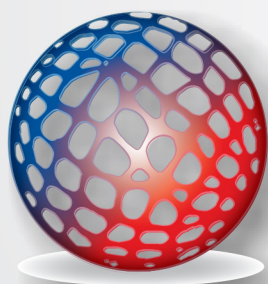
7th International Wasog Conference on Diffuse Parenchymal Lung Diseases.

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VAGAS LIMITADAS

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X CONGRESSO BRASILEIRO DE ASMA
VI CONGRESSOS BRASILEIROS DE DPOC E TABAGISMO
XVI CONGRESSO PAULISTA DE PNEUMOLOGIA E TISIOLOGIA

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Expediente

BRAZILIAN THORACIC SOCIETY

Sumário/Contents

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2015—another step along the road in a 40-year journey...

2015 — mais um passo em um caminho de 40 anos...

Rogério Souza

This is a special year for the Brazilian Journal of Pulmonology (BJP); in October, the BJP will turn 40.[1] Dates such as this are particularly significant, given that they lead us to reflect on many of the aspects related to the existence of the BJP: its history; its current relevance; and its prospects.

The BJP was founded in 1975, and the fact that it continues its journey today is undoubtedly due to the continuous efforts of numerous colleagues who, directly or indirectly, have sought to make the Journal function as a great common denominator linking all members of the respiratory medicine community. This process has been spearheaded by a group of brave editors whose efforts have led the BJP to great achievements: Manoel Lopes dos Santos (1975-6); Bruno Carlos Palombini (1976-8); Carlos Frazzatto Junior (1978-82); José Roberto de Brito Jardim (1982-6); Miguel Bogossian (1986-90); Nelson Morrone (1990-4); Carlos Alberto de Castro Pereira (1994-8); Thais Helena Abrahão Tomaz Queluz (1998-2002); Geraldo Lorenzi Filho (2002-4); José Antônio Baddini Martinez (2004-10); and, most recently, Carlos Roberto Ribeiro Carvalho (2010-4), all of whom have contributed to making the BJP the most important scientific journal in the respiratory field in Latin America and one of the most important scientific journals in Brazil. Such a feat gives us a measure of the responsibility we all have to our Journal henceforward.

In recent decades, the BJP was indexed for SciELO (2002) and, subsequently, for PubMed/MEDLINE (2006), which has greatly increased the visibility of the Journal and therefore the number of articles submitted, particularly after it was indexed for the Thomson Reuters Institute for Scientific Information Web of Science and its first impact factor appeared in Journal Citation Reports.[2] We have recently been penalized by having our impact factor temporarily suspended, a fact that will affect us in the next evaluation.[3] However, we have to bear in mind that this metric associated with scientific publication should be understood within its surrounding context rather than as a single number. In particular, the BJP has

two very clear functions: to be a publication of quality, providing a vehicle for scientific production in the field of respiratory medicine, especially in Brazil but also worldwide, and to be the major instrument for the continuing education of pulmonologists in Brazil. For the latter mission, the commitment is to reach into the daily lives of its readers through review articles that reflect the necessities of daily clinical practice in the respiratory field. It is for the dissemination of scientific production that we will use common editorial metrics, such as the impact factor. Such metrics, despite their limitations, allow editorial policy planning, with course changes when necessary, in order to increase the national and international visibility of the Journal, thereby attracting the very best science in the field. To that end, several steps have been taken with a view toward increasing the international exposure of the BJP, among which is the fact that, since 2014, the Journal has been available on PubMed Central, an open archive of the U.S. National Institutes of Health National Library of Medicine, making it possible to access the full-text articles published by the BJP (in English) directly via the PubMed search function.[4]

We will now make all articles accepted by the BJP available online ahead of print, in order to maximize the exposure time of our publications. In parallel, all BJP content will be screened for plagiarism with the same tools used by the major scientific journals in the medical field. With this screening, along with the exposure, the trustworthiness of the content of the BJP will also increase significantly.

Although the responsibility of managing the BJP is huge, standing on the shoulders of those who have made the Journal so solid makes the path much smoother. The aforementioned changes are aimed at preparing us for further growth. In addition, another very important change deserves special mention. The board of associate editors of the BJP has grown significantly. In advance, I thank all the editors who have embarked on the project for the next four-year term of editorship of the BJP, which begins now. The participation

of such a significant body of researchers in the editorship of the Journal undoubtedly allows a closer relationship between the BJP and major research groups, in Brazil and around the world. It also allows the BJP to play its aforementioned role in the continuing education of respiratory medicine professionals working in Brazil, particularly those who are not affiliated with educational institutions. The selection of the topics of greatest interest to all kinds of readers will come to be shared by a group that is representative of the various fields of study in respiratory medicine, potentially enhancing the scope of the Journal.

The ultimate goal for the next four years is to increase the representativeness of the BJP, not only via its role of disseminating scientific knowledge, which is to be measured by various existing metrics, but also via the role it plays in the education of health professionals in Brazil, which is to be measured by the interest in the different areas of the Journal, on the basis of the number of logins/downloads and requested reprints. Let us hope that the celebrations of and reflections on the last 40 years of BJP history will lead us steadily toward a 2015 full of achievements.

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Rogério Souza
Editor-in-Chief of the Brazilian Journal of Pulmonology

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References

1. Santos ML. Brazilian Journal of Pulmonology: thirty years of history. J Bras Pneumol. 2005;31(5):i. http://dx.doi.org/10.1590/S1806-37132005000500001

2. Carvalho CR. Publications in the Brazilian Journal of Pulmonology. J Bras Pneumol. 2013;39(1):1-4. http://dx.doi.org/10.1590/S1806-37132013000100001

3. Carvalho CR. The Brazilian Journal of Pulmonology and international databases. J Bras Pneumol. 2013;39(5):529-31. http://dx.doi.org/10.1590/S1806-37132013000500001

4. Carvalho CR, Baldi BG, Jardim CV, Caruso P, Souza R. New steps for the international consolidation of the Brazilian Journal of Pulmonology. J Bras Pneumol. 2014;40(4):325-6. http://dx.doi.org/10.1590/S1806-37132014000400001

A workshop on asthma management programs and centers in Brazil: reviewing and explaining concepts*

Programas e centros de atenção a asmáticos no Brasil; uma oficina de trabalho: revisitando e explicitando conceitos

Rafael Stelmach, Alcindo Cerci Neto, Ana Cristina de Carvalho Fernandez Fonseca, Eduardo Vieira Ponte, Gerardo Alves, Ildely Niedia Araujo-Costa, et al.

Abstract

Objective: To report the results of a workshop regarding asthma management programs and centers (AMPCs) in Brazil, so that they can be used as a tool for the improvement and advancement of current and future AMPCs. **Methods:** The workshop consisted of five presentations and the corresponding group discussions. The working groups discussed the following themes: implementation of asthma management strategies; human resources needed for AMPCs; financial resources needed for AMPCs; and operational maintenance of AMPCs. **Results:** The workshop involved 39 participants, from all regions of the country, representing associations of asthma patients (n = 3), universities (n = 7), and AMPCs (n = 29). We found a direct relationship between a lack of planning and the failure of AMPCs. Based on the experiences reported during the workshop, the common assumptions about AMPCs in Brazil were the importance of raising awareness of managers; greater community participation; interdependence between primary care and specialized care; awareness of regionalization; and use of medications available in the public health system. **Conclusions:** Brazil already has a core of experience in the area of asthma management programs. The implementation of strategies for the management of chronic respiratory disease and their incorporation into health care system protocols would seem to be a natural progression. However, there is minimal experience in this area. Joint efforts by individuals with expertise in AMPCs could promote the implementation of asthma management strategies, thus speeding the creation of treatment networks, which might have a multiplier effect, precluding the need for isolated centers to start from zero.

Keywords: Asthma; Academic medical centers; Area health education centers; Health planning organizations; Regional medical programs; Managed care programs.

Resumo

Objetivo: Relatar os resultados de uma oficina de trabalho sobre programas e centros de atenção a asmáticos (PCAAs) no Brasil para que possam servir como instrumento para melhoria e avanço dos PCAAs existentes e criação de novos. **Métodos:** A oficina de trabalho constituiu-se de cinco apresentações e discussões em grupos. Os grupos de trabalho discutiram os seguintes temas: implementação de uma linha de cuidado em asma; recursos humanos necessários para os PCAA; recursos necessários para financiar os PCAA; e manutenção do funcionamento dos PCAAs. **Resultados:** A oficina envolveu 39 participantes de todas as regiões do país, representando associações de asmáticos (n = 3), centros universitários (n = 7) e PCAAs (n = 29). Evidenciou-se uma relação direta entre a ausência de planejamento e o insucesso dos PCAAs. Com base nas experiências brasileiras elencadas durante a oficina, as premissas comuns foram a importância da sensibilização do gestor, maior participação da comunidade, interdependência entre a atenção primária e a especializada, observação da regionalização e utilização dos medicamentos disponíveis no sistema público de saúde. **Conclusões:** O Brasil já tem um núcleo de experiências na área programática da asma. A implementação de uma linha de cuidado em doenças respiratórias crônicas e sua inclusão nas redes de saúde parecem ser o caminho natural. Porém, a experiência nessa área ainda é pequena. Agregar pessoas com experiência nos PCAAs na elaboração da linha de cuidado em asma encurtaria tempo na criação de redes de atenção com possível efeito multiplicador, evitando que se partisse do zero em cada local isolado.

Descritores: Asma; Centros médicos acadêmicos; Centros educacionais de áreas de saúde; Organizações de planejamento em saúde; Programas médicos regionais; Programas de assistência gerenciada.

Introduction

Some asthma patient management programs and centers that are currently in operation in Brazil are coming of age. In an editorial, Holanda[1] reported results of questionnaires on Asthma Management Programs and Centers (AMPCs) in Brazil, completed by 16 members of the Brazilian Thoracic Association (BTA) or regional affiliates. At the time, 14 AMPCs (87.5%) confirmed that they were in regular operation, 10 of which had been established in the 1990s. Looking back, the responses regarding asthma management seem alarming: inhaled medications were unavailable (there were only oral medications); treatment demand was higher than treatment availability; and there were no outpatient clinics specializing in asthma.

Many AMPCs were created as a result of the dissemination of the first national and international guidelines for the management of asthma, published in the same decade. Therefore, those guidelines prompted the holding of the First and Second Brazilian Conferences on Asthma in 1997 and 1999, respectively. The unavailability of inhaled corticosteroids (ICs) in public institutions contradicted the cornerstone of the treatment of persistent asthma, derived from the guidelines. Pioneers of that time include the AMPCs in the cities of Belo Horizonte, Fortaleza, and São Paulo, which already showed that educating patients decreased the number of hospitalizations and improved patient quality of life.[1,2]

One group of authors[2] prepared a timeline of the evolution of public policies and AMPCs in Brazil since 1996, showing that, in 1998, the National Drug Policy was created, which led to the dispensation of medications for asthma control. This provision stimulated and gave support to the creation of new programs and required the implementation of referral centers.[2] It is not by chance that the *Carta de Salvador* (Salvador Charter),[3] urging the implementation of the National Asthma Control Program, was formulated in 2001. The cities of Porto Alegre, Goiânia, Londrina, Niterói, Salvador, Feira de Santana, Rio de Janeiro, and Vitória established their AMPCs at the same time as decrees regulating the allocation of federal resources to health care services were being issued.[2] At that time, in addition to ensuring care for asthma patients, some AMPCs stood out for their scientific production, others stood out for providing training to professionals from different areas, and others stood out for expanding to small municipalities, decentralizing activities.

In 2007, an editorial[4] presented an account of the decade and highlighted the need for professional training and funding to advance the quality of care by improving AMPCs. Examples of asthma programs in Brazil were obtained in 2008, by analyzing the responses to the forms sent to BTA members and members of the Brazilian Association of Allergists and Immunologists.[5] Of 55 services that reported having a systematized program, 11 (20%) did not respond to the structural questions and 27 (49%) were excluded from the analysis (17 treated severe asthma and 10 had had the program for less than two years). All 17 programs analyzed received public funding for their maintenance: 4 (23%) received state funding exclusively, whereas 13 (77%) received state and municipal funding. There were no programs in northern Brazil. All 17 programs had referral centers with specialists, and 47% developed educational activities (lectures or individual visits) within the community. In addition, 47% provided home visits by nurses, and 41% adopted public health strategies, such as family health care, outreach, humanizing practices, and visits by community health care agents. That study[5] showed that, from 2003 onward, the number of programs increased significantly, as a result of the availability of full public funding for the purchase of asthma medications.

Some successful programs no longer exist because of political and administrative changes. However, it can be stated that there has been no dissemination of programs across the country. There are still fewer than five dozen programs, as mentioned above. Most are supported by the dedication of some individuals—experts in their field—and often with resources from funding agencies, partnerships with the private sector, or both. In the majority of localities, they have not become programs or management strategies of the municipal or state departments of health, especially since, as yet, the Brazilian National Ministry of Health itself has not prioritized management strategies for chronic respiratory diseases.

Between 1991 and 2010, the epidemiologic picture changed, as a result of the growth of the Brazilian population at a rate of 20 million per decade. The population jumped from 146.8 million in 1991 to 190.7 million in 2010.[6] This

http://dx.doi.org/10.1590/S1806-37132015000100002

means that there was an increase in the number of asthma patients. Conversely, the number of hospitalizations for asthma via the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System) decreased from 400,000 per year to fewer than 200,000 per year between 2000 and 2012,[7] with a disproportionate decrease of 30% in the expenditures for such hospitalizations (110 million Brazilian reals vs. 80 million Brazilian reals). It is correct to state that the asthma centers and programs helped this reduction in the number of hospitalizations. In addition, they encouraged the changes made by the laws and national regulations that initially led to the decentralization of payment of costs of asthma and rhinitis medications, as well as to the publication of the Primary Care Guidebook – rhinitis , asthma, and COPD[8] and, more recently, of the revised Clinical Protocol and Therapeutic Guidelines – asthma.[9] Because of the high prevalence of COPD, which is a mandatory differential diagnosis for asthma, COPD care was combined with asthma care in adults in some centers, in addition to being standardized at the federal level.[10] Given the regulation of the basic (i.e. municipal) and specialized (i.e. state) components of pharmaceutical care, as well as the free provision of basic asthma medications at enrolled pharmacies since 2012, it can be stated that there already is adequate public funding.[2] However, the population's demands for more resources/materials for the treatment of chronic respiratory diseases have become a reality for public and private health, including via litigation.[11] Another change in public health has been the increased value placed on the family health program strategy. According to the Brazilian National Ministry of Health,[12] half of the Brazilian population receive some care through that strategy, and one of the current developments is the controversial program of importation of physicians. Conversely, several national and international studies have shown that asthma is not controlled in more than 50% of the patients evaluated,[13] which can be confirmed by the still low use of ICs.[14]

What to do to provide care for those who remain unassisted and to continue to decrease asthma-related morbidity and mortality in Brazil is the question. The Global Initiative for Asthma (GINA)[15] recommends that, by 2015, there should be fewer than 100,000 hospitalizations per year for asthma in Brazil. It must be borne is mind that, despite the decrease in the number of hospitalizations, official statistics show that the number of deaths from asthma (3,000 deaths per year) has remained unchanged.[7] How to continue the history of AMPCs, making them a reference in education and care, is the challenge ahead. How to multiply them (physically or conceptually) is a challenge and a requirement. In an attempt to answer these questions, it was proposed that a workshop on AMPCs in Brazil be held. The objective of the present study was to report the results of this workshop so that they can be used as a tool for the improvement and advancement of current centers and programs, as well as for the establishment of new ones.

Methods

Using a list of AMPCs that were identified in surveys conducted in 2000, 2008, and 2013 (the last survey has not been published), four coordinators of AMPCs that have been in operation since the 1990s selected health professionals with related activities throughout Brazil. The geographic distribution, lifetime (continuity), and infrastructure of AMPCs were taken into consideration, as were their scientific production, training of staff specializing in chronic respiratory diseases, and successful or innovative experiences in the area. Some professionals involved in tertiary care (severe asthma), as well as individuals who were in charge of associations of asthma patients and had health training, were also selected. In addition, physicians, nurses, and pharmacists who were directly involved in the processes in AMPCs and who preferably did not perform program management were invited. Two workshop coordinators made a list of 48 guests after analysis of AMPCs, as well as of associations of patients in the states of Rio de Janeiro and São Paulo.

The objectives proposed for the workshop were as follows:
- Compile successful experiences in AMPCs in Brazil and the difficulties in implementing asthma management strategies in the SUS.
- Outline the current state of initiatives in asthma in Brazil in their various phases (planning and regional integration; professional training and standardization; funding and management; expansion and consolidation; and national guidelines for asthma programs).

- Find and propose solutions to problems associated with the development of the AMPCs that are already in operation in the country.
- Develop a practical manual for the implementation of program activities and centers of excellence for the treatment of asthma.

The workshop agenda was designed to favor group work. The coordinators defined the proposed themes for discussion. Presentations on specific issues served as a basis for the group discussions. Each group had two coordinators, who were in charge of recording the discussions and reporting them at plenary sessions. Chart 1 presents a summary of the workshop program.

The group discussions were recorded in real time by a company specializing in editing for events. The results were systematized by combining the group reports, the notes made by the (workshop and group) coordinators, and the text prepared by the editing company. The results are presented by group discussion topic.

Results

Of 48 guests, 39 attended the event, which was held in the city of São Paulo and lasted eight hours. All regions of the country were represented (the Northern, Central West, Northeastern, Southern, and Southeastern regions had 1, 2, 8, 11, and 17 representatives, respectively). The group of professionals consisted of 13 pulmonologists, 8 pediatric pulmonologists, 6 allergists/immunologists, 6 pediatricians (2 of whom were allergologists), 2 family/community physicians, 3 pharmacists, and 1 nurse. The associations of asthma patients had 3 representatives present. Seven professionals represented university (secondary/tertiary) referral centers, and 29 represented AMPCs. Although three of those

Chart 1 – Outline of the workshop on asthma management programs and centers.

Outline content
Opening remarks
Situation at the time of the event
Asthma and Public Health – a current overview
Asthma management program activities – lines of conduct
Primary care in respiratory programs: matrix-like planning in asthma/COPD
Difficulties of/solutions for highly demanded asthma programs
Formation of working groups based on guiding principles
Difficulties in implementing asthma management strategies
Lack of planning
Unawareness of the regional context
Inadequate regional integration models
Lack of partnerships
Securing human resources for asthma programs
Importance of training
Who should be trained?
Is it important to create regional protocols?
How can the community be involved in the process?
The role of referral centers in the development of human resources
Seeking financial resources for asthma programs through public/private/academic sector cooperation
What are the current funding sources?
How can access to those resources be gained?
How and who should manage the resources?
Where and how should the resources be spent? (education, training, medications?)
Operational maintenance of asthma programs
The asthma program is operational, what now?
How can the experience be expanded and replicated?
Is it worthwhile to include other diseases?
Presentation of the conclusions of the working groups
Debates

centers/AMPCs had private management, all were directed to SUS.

The results of the study groups were systematized and are described as follows:

Difficulties in implementing asthma management strategies

Lack of planning

- Strategic planning is critical in implementing asthma management strategies, in order to minimize potential implementation difficulties and maximize community and public manager awareness.
- Through planning, public managers are committed to political and financial support, even when there are local political changes.
- In order to maintain the support from public managers, asthma management strategies should have an appropriate cost-benefit ratio and prioritize the free provision of outpatient asthma medications, because this reduces hospitalization expenditures and increases the productivity of patients and health professionals.
- It is important to estimate the number of patients who will be reached by the intervention. Management strategies that prioritize primary care help a large volume of patients who, individually, do not use the health care system very often. When management strategies prioritize secondary care, they will help a smaller volume of patients who individually use many health resources. In the long run, no level of care should be excluded, and there should be mechanisms to allow patients to seek treatment networks or webs according to the behavior of their disease.
- Planning focused on the development of continuous data collection tools provides indicators that can be used to measure the benefits and impact of those activities in public health.
- Civil society and medical societies must work together to avoid setbacks in the treatment of asthma patients, and,

therefore, public awareness should be raised.

- Medical specialty societies and patient associations have a very positive record in fostering the implementation of asthma management strategies.
- Currently, asthma programs are organized around individuals, and there is a high risk of loss of continuity.

Regional context unawareness / inadequate regional integration models

- Asthma management strategies should respect the heterogeneity of the country. There is already a minimal health care system that reaches almost the entire country—primary care clinics (PCCs) and family health program teams/strategies—which should be prioritized.
- Asthma management strategies should take advantage of the structure that is available. Specialized centers are indispensable to training primary care teams without experience in asthma and to supporting patients who are refractory to treatment, while also making that structure available to smaller municipalities (in the region).

Lack of partnerships

- In order to implement and maintain asthma management strategies, it is necessary to have support from the public/state sector, the private sector (i.e., schools, pharmaceutical industries, the media, and health insurance plans), and the third sector (i.e., universities, religious institutions, nongovernmental organizations, foundations, associations, etc.).
- The physical structure, the purchase of medications, and the health teams are the responsibility of municipalities and states. The private sector and the third sector can contribute by disseminating information, providing technological knowledge, and facilitating public/state sector activities. These contributions can mainly take the form of scientific meetings for health teams, donation of spirometers, support for forming associations of asthma patients, media dissemination of information about

asthma to the lay public, and commitment for selling medications to the public sector at the lowest price possible.

- The use of volunteers should be encouraged. Presentations in schools and communities given by volunteers have significant impact, according to experiences in the city of São Paulo. It is of note that volunteer activities are not regular and should be planned as short-term.

Securing human resources for AMPCs

Importance of training

- Continuing training of all categories of health professionals at all levels of care is necessary so that professionals working in asthma care know how to identify, classify, and manage patients appropriately, thereby reducing asthma-related morbidity and mortality, as well as improving the quality of life of patients and their family members.
- In addition to health professionals, it is of paramount importance to train patients and their family members in recognizing the disease, the periods of exacerbation, and the forms of treatment, therefore preventing complications.
- Currently, the focus of public health is the Family Health Program Strategy, which is responsible for the holistic care of individuals. The objective is to train primary care professionals so that they can identify people with asthma, classify them in accordance with the clinical protocols, and manage them, in order to reduce the number of unnecessary referrals to secondary care and not to place an additional burden on the health system.
- In addition to training, it is important that the network be under continuing supervision for the maintenance of appropriate care, with qualified referrals, well-defined network flows, and monitoring of local indicators.

Who should be trained?

- Training should be attended by the multidisciplinary team together as a group, and a piece of information that is shared by all categories should be used in demonstrating the role of each individual in patient care. Techniques such as matrix-like planning can make the function of each professional in daily practice clearer. Any trained professional can be a local tutor.
- Professionals at referral centers should also be trained to receive, accommodate, and treat patients in accordance with specialized care protocols.
- The creation of regional centers could enable training and consulting anywhere in the country through partnerships, preventing extensive traveling within the country. Professionals from societies, institutions, and universities who are associated with the asthma problem in our communities can be part of those centers.

Is it important to create regional protocols?

- With regard to the creation of regional protocols, it is of note that the current national and international patient care guidelines are applicable to all centers. Indeed, It is necessary to create flows and organize health care services according to local contexts.

How can the community be involved in the process?

- A community that is aware of the risks and costs of illness, and that knows that there are resources to reduce them, mobilizes with public authorities to try to improve care for users.
- Community involvement should be broad, considering individuals with or without asthma, but with an emphasis on the asthma community, with includes patients and their family members.
- Knowledge about asthma and asthma management strategies should be disseminated widely, and this can be made possible through local health councils and through local/regional media (television, radios, churches, and schools). The dissemination of information

through widely accessed electronic media such as social networks reaches large populations.

- Emphasize to patients that they are responsible for demanding complete, quality care, which includes professionals who provide appropriate care, provision of necessary materials, and continuing education. This responsibility cannot be assumed only by health professionals.
- Children should start receiving asthma education early, which, in addition to strengthening family ties in terms of education, encourages adherence to treatment.

The role of referral centers in the development of human resources

- During training, referral centers are responsible for passing on information regarding patient referral flow and asthma management strategy steps to the entire system. This knowledge should be shared by all professionals working in the system, from primary care professionals to professionals working in referral centers, whether they are regional/secondary or tertiary centers.
- Referral centers are also responsible for providing information to primary care professionals and for, together with those professionals, defining criteria for patient referral to/from referral centers and criteria for patient follow-up. Standardization of patient follow-up and management, as well as of referral and counter-referral models, facilitates dialogue.

Seeking financial resources for asthma programs through public/private/academic sector cooperation

What are the current funding sources?

- From a broad perspective, funding is partially taken care of, especially when it comes to medications. The lack of funding implies discontinuity of activities and loss of motivation.
- The federal government makes asthma medications available through the special drugs program and the "Popular

Pharmacy" program. Some municipalities contribute by making ICs and short-acting bronchodilators available at PCCs.

- There is a need for an alignment between what is proposed in the guidelines/strategies and what in fact there is to treat patients and control asthma.

How can access to those resources be gained?

- The group discussions evidenced the need for the current forms of funding and for alternatives to be further explained in a document prepared by public health specialists with a deep understanding of the subject. This document would be produced by specialist societies or organizations/associations related to asthma.
- There are forms and sources of funding that are unknown to the group.
- The provision of special medications, with the addition of long-acting β_2 agonists, was an advance; however, in some programs, this provision is not far reaching, because it is focused on people (it is not standardized).

How and who should manage the resources?

- Social control is very important because it fosters the continuity of the program.
- The raising and allocation of resources should be based on technical rather than on political criteria.
- A joint management strategy with the family health program should be pursued. Since primary care is a priority and resources are directed to it, it is not feasible to have resources available for the asthma program unless there is integrated patient care. There is no money specifically for asthma, but there is money for primary care.
- In addition, there are funding sources other than the federal government, such as state and municipal foundations, through which it is possible to obtain additional resources.

Where and how should the resources be spent?

- It was concluded that there is no conflict between the recommendations in national and international guidelines and the medications provided to patients. Medications should be addressed in all stages of planning guidelines in the program.
- Funding for asthma education is as necessary as is funding for other activities. The resource exists, but it is imperative to understand and propose ways to apply for it.

Operational maintenance of asthma programs

The present work group chose to merge the three questions that should be included in the program—"The asthma program is operational, what now?"; "How can the experience be expanded and replicated?"; and "Is it worthwhile to include other diseases?—into a single theme, which is described below.

Strategies for maintaining, expanding, and replicating asthma programs

- AMPCs are characterized as a set of pre-defined activities, objectives, and goals that will meet the needs of a population.
- The maintenance of AMPCs requires the following: knowledge of the local context; multidisciplinary coordination and institutional programs; greater awareness and continuing updating of professionals; dissemination of activities; and participation of the population.
- It was identified that comprehensiveness of care is important in individual care; however, when it comes to programs, maintaining the focus on care for people with asthma is critical. There should be integration with programs targeted at other conditions, such as smoking and COPD. For instance, smoking family members of children with asthma should be advised and referred to smoking cessation groups. The management of allergic rhinitis, however, should be addressed in asthma clinical protocols,

given the prevalent association between rhinitis and asthma.
- Knowledge of the local context, together with definition of the area of operation and delimitation of the target population, favors the maintenance of the process. Cultural issues should be part of that knowledge and should guide activities that respect diversity.
- Program coordination should be multidisciplinary (pharmacists, family physicians, specialists, physical therapists, etc.), which provides different perspectives on the program and facilitates informed planning decisions based on the local context.
- Personal ownership—"So-and-so's program"—should be avoided. The program, whenever possible, must have a name of its own and institutional guidelines.
- Epidemiological data, such as prevalence and impact of asthma, should be used to raise awareness of and update professionals, being part of the educational process.
- Protocols or guidelines should be adapted for local use on the basis of current strategies, such as those of GINA and of the BTA. These protocols should include the different resources, whether structural or human, of primary care (PCCs), secondary care (specialty outpatient clinics), or tertiary care (emergency rooms and hospitals), with well-defined referral criteria and with an emphasis on treatment networks.
- The activities of the program and the assessment indicators should be disseminated to the population, managers, and directly involved professionals, as well as to the academic community (through conferences, symposia and publications). The information should be clear and objective. It is considered important to include communication techniques in the training of professionals. These individuals and groups can pass on technical information to the population, both individually and collectively, in health care clinics, local health councils, schools, associations of asthma patients, etc. The

dissemination can be achieved through electronic means, newsletters, and more objective reports.

- It is important to provide managers with updated local epidemiological data and results for cost reduction and improvement in the quality of life of patients and their family members, as well as data regarding the involvement of the population.

Discussion

The results of the present study confirm the importance of planning. We found a direct relationship between a lack of planning and the failure of asthma programs in their various phases (design, implementation, and maintenance). In the experiences reported during the workshop, there were shared assumptions in the planning phase of AMPCs in Brazil: greater awareness of managers; greater community participation; interdependence between primary care and specialized care; awareness of the regional context; and use of medications available in the public health system for the treatment of asthma. This is consistent with the medical literature,[16,17] but there are some differences in the hierarchy of these assumptions.

The literature shows that one of the essential conditions for the implementation and maintenance of asthma programs is previous planning. In 2012, one group of authors[16] highlighted the importance of and the need for the creation of a planning group that, from the beginning, involves all segments that will play a role in the asthma programs, including managers. This critical step of the process should be guided by knowledge of possible difficulties of the health care system, which are accessed through established indices.[16,18]

The GINA guidelines for improving care in asthma[16] and the recommendations published by the BTA[17] are currently two of the major sources of technical information and methods for implementation of asthma programs. However, hearing the players themselves in their work processes, which was made possible by the present study, revealed a scenario is that differs from those guidelines/recommendations in some aspects and complies with them in others. The workshop format in the present study allowed a very productive exchange of information among the various initiatives in Brazil and contributes to making up for the lack of scientific publications.

The results of the present study made it clear that the population is the major player in the process, because, in addition to being the object of the intervention, it is the major element that should initiate and monitor the program implementation process. Various studies have shown that interventions in the community, in order to provide greater educational and scientific support, lead to improved results.[19] Social participation does not consist only of a monitoring role, but also of joint and multidisciplinary initiatives, such as dissemination of social knowledge.

It is also clear from the results that awareness of and decision making by public managers are determining factors for the success or failure of program activities. This is a characteristic of Brazilian society and is not related directly to health, but rather to politics,[20] especially since the asthma interventions in the community that are mentioned in the present study[5] were designed in state or municipal departments of health or in public universities. It is essential to understand that the role of the programs is both technical and political, which requires knowledge of legislation, system organization, public health strategies, etc.[17] The issue of participation of managers permeates continuity solutions that can directly affect program maintenance. The involvement of collegiate bodies or the conversion of programs into state/municipal laws or decrees, such as the newly launched *Programa Respira Minas* (Breathe, Minas Program),[21] reduces the possibility of discontinuity.

The understanding that the various levels of care should work jointly and in a coordinated manner was reinforced. The notion of interdisciplinary and multidisciplinary teams assuming a role in management strategies is internationally well known, and the singularity of professional categories is recognized, using these unique characteristics in order to improve team efficacy.[18,22,23]

Referral centers are support centers for patients who are more severely ill or for those who require technological or therapeutic resources. In addition, they can be responsible for training activities and for continuing and permanent education. In the models in Brazil, referral centers are also centers of program planning and management. Currently, managers invest most health resources in primary care, which can cause imbalance in

management strategies. The balance between the different levels of care is an essential condition for any management strategy.[17] According to the results of the present study, in centers where there are no specialists, it is necessary that specialists be available regionally.

Another important component in the implementation of AMPCs is the process of education through training of all health professionals[24] and of patients themselves. One group of authors showed that the implementation of education programs leads to a reduction in asthma attacks, decreasing the number of hospitalizations and emergency room visits, as well as bringing about improvement in the quality of life of asthma patients.[25]

Continuing multidisciplinary training of primary care professionals has been shown to have a direct relationship with fewer asthma-related hospitalizations and better-informed referrals to specialties[19-22] The vast majority of primary care professionals in Canada preferred training based on a combination of didactic lecture and clinical case discussion.[26] More rational prescription of medications, well-structured action plans, and the proper use of spirometry led to improved care for asthma patients. In addition, according to the participants in the present study, professional training should address management strategies, especially referral and counter-referral criteria and flows.

The Clinical Protocol and Therapeutic Guidelines[9] available in the SUS includes almost all therapeutic classes for asthma treatment, but their indications are for different situations than those recognized by national and international guidelines.[15,27] Nevertheless, the workshop reiterated that it is not necessary to create new clinical protocols (also known as guidelines for asthma), but only to adapt them to local contexts and medical contexts.

There are resources for the purchase of medications (municipal resources) and for medical specialties (mostly state resources).[28,29] The lack of resources—or the unawareness of their availability—is often cited as a limiting factor for the development of program implementation, but there are various activities that can be developed without financial resources.[16]

The involvement of other professionals and the transformation of programs into institutional policies rather than people-centered policies are key factors for success. Success has already been achieved in asthma programs in the cities of Belo Horizonte and Salvador,[30-33] where there are several publications reporting national and international indicators of quality.

It was concluded that, even without appropriate dissemination, Brazil already has a core of experience in the area of asthma management programs, through local and regional activities, as well as activities in universities. Despite the fact that the movement for the creation of asthma programs has contributed to the current design of funding for treatment of the disease and has certainly influenced the epidemiological change regarding the disease, there has been no proliferation of AMPCs. Since 2003, the number of AMPCs in operation has remained virtually unchanged. Although this is not a phenomenon occurring just in Brazil,[16] the national experience of AMPCs is sufficiently mature and has a critical mass of experienced professionals to come up with proposals[5] for change.

The implementation of national strategies for the management of respiratory diseases and their incorporation into health care system protocols would seem to be a natural progression. However, there is minimal experience in management strategies in this area. Joint efforts by individuals, such as the present workshop participants, with expertise in AMPCs and availability to go to interested centers, who could act as facilitators to developing standards and methods and who could raise awareness of managers, would speed the creation of treatment networks and have a multiplier effect, thus precluding the need for isolated centers to start from zero.

References

1. Holanda MA. Asmáticos brasileiros: o tratamento desejado. J Pneumol. 2000;26(3):vii-ix. http://dx.doi.org/10.1590/S0102-35862000000300001

2. Amaral LM, Palma PV, Leite IC. Evolution of public policies and programs for asthma control in Brazil from the perspective of consensus guidelines. J Bras Pneumol. 2012;38(4):518-25. http://dx.doi.org/10.1590/S1806-37132012000400015

3. Silva LC, Freire LM, Mendes NF, Lopes AC, Cruz A. Carta de Salvador. J Pneumol. 2002;28 Suppl 1:S2. http://dx.doi.org/10.1590/S0102-35862002000700002

4. Cerci Neto A, Zamboni MM, Holanda MA. Open letter in favor of the creation of asthma programs in Brazil. J Bras Pneumol. 2007;33(2):ix-x. http://dx.doi.org/10.1590/S1806-37132007000200001

5. Cerci Neto A, Ferreira Filho OF, Bueno T. Brazilian examples of programs for the control of asthma. J Bras

Pneumol. 2008;34(2):103-6. http://dx.doi.org/10.1590/S1806-37132008000200007

6. Instituto Brasileiro de Geografia e Estatística [homepage on the Internet]. Brasília: IBGE [cited 2014 Jun 1]. Estatística população 2012. Available from: http://www.ibge.gov.br/home

7. DATASUS [homepage on the Internet]. Brasília: Ministério da Saúde [cited 2014 Jun 1]. Informações epidemiológicas de morbidade (TABNET) e mortalidade. Available from: http://www2.datasus.gov.br/DATASUS

8. Brasil. Ministério da Saúde. Secretaria de Políticas de Saúde. Departamento de Atenção Básica. Doenças Respiratórias Crônicas: cadernos de atenção básica, 25. Série A. Normas e Manuais Técnicos. Brasília: Ministério da Saúde; 2010.

9. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Portaria no. 709, de 17 de dezembro de 2010. Aprova o Protocolo Clínico e Diretrizes Terapêuticas - Asma. Brasília: Diário Oficial da União, 22 dez 2010; n. 244, Sec 1:99.

10. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Portaria no. 609, de 6 de junho de 2013. Aprova o Protocolo Clínico e Diretrizes Terapêuticas - Doença Pulmonar Obstrutiva Crônica. Brasília: Diário Oficial da União, 6 jun 2013; n. 108, Sec 1:36.

11. Pepe VL, Figueiredo TA, Simas L, Osorio-de-Castro CG, Ventura M. A judicialização da saúde e os novos desafios da gestão da assistência farmacêutica. Ciên Saude Coletiva. 2010;15(5):2405-14. http://dx.doi.org/10.1590/S1413-81232010000500015

12. Brasil. Ministério da Saúde. Departamento de Atenção Básica. [homepage on the Internet]. Brasília: DAB [cited 2014 Jun 1]. Atenção Básica e a Saúde da Família. Available from: http://dab.saude.gov.br/atencaobasica.php

13. Gold LS, Montealegre F, Allen-Ramey FC, Jardim J, Smith N, Sansores R, et al. Level of asthma control and healthcare utilization in Latin America. Allergy. 2013;68(11):1463-6. http://dx.doi.org/10.1111/all.12237

14. Stelmach R. Estimativa do percentual de pacientes tratados com corticosteroide inalado (Beclometasona HFA) pelo Sistema Único de Saúde (SUS) e no sistema Farmácia Popular em Minas Gerais, São Paulo e Rio Grande do Sul. Comunicação pessoal. São Paulo: Chiesi Farmacêutica; 2014.

15. Global Initiative for Asthma – GINA [homepage on the Internet]. Bethesda: Global Initiative for Asthma. [cited 2014 Jun 1]. Available from: www.ginasthma.org

16. Boulet LP, FitzGerald JM, Levy ML, Cruz AA, Pedersen S, Haahtela T, Bateman ED. A guide to the translation of the Global Initiative for Asthma (GINA) strategy into improved care. Eur Respir J. 2012;39(5):1220-9. http://dx.doi.org/10.1183/09031936.00184511

17. Sociedade Brasileira de Pneumologia e Tisiologia. Pratica Pneumológica: Ações Programáticas em Pneumologia. Brasília: SBPT/GEN; 2012.

18. Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, et al. A 10 year asthma programme in Finland: major change for the better. Thorax, 2006;61(8):663-70. http://dx.doi.org/10.1136/thx.2005.055699

19. Cerci Neto A, organizador. Asma em saúde pública. São Paulo: Manole; 2007.

20. Brasil. Poder Legislativo. Lei Orgânica da Saúde no 8080, de 19 de setembro de 1990. Brasília: Diário Oficial da União, 20 set 1990; Sec 1:18055.

21. Governo do Estado de Minas Gerais. Secretaria do Estado da Saúde. Aprova a instituição do Programa Respira Minas, no âmbito do Estado de Minas Gerais. Deliberação CIB-SUS/MG no 1.861, 01 de julho de 2014. Belo Horizonte: Diário Oficial do Estado de Minas Gerais, 3 jul 2014; Sec 1:17.

22. Cerci Neto A. Mudança no perfil do manejo da asma em uma cidade brasileira de médio porte após programa estruturado: dados após quatro anos de implantação [thesis]. Londrina: Universidade Estadual de Londrina; 2009.

23. Lozano P, Finkelstein JA, Carey VJ, Wagner EH, Inui TS, Fuhlbrigge AL, et al. A multisite randomized trial of the effects of physician education and organizational change in chronic-asthma care health: outcomes of the Pediatric Asthma Care Patient Outcomes Research Team II Study. Arch Pediatr Adolesc Med. 2004;158(9):875-83. http://dx.doi.org/10.1001/archpedi.158.9.875

24. Oliveira MA, Muniz MT, Santos LA, Faresin SM, Fernandes AL. Custo-efetividade de programa de educação para adultos asmáticos atendidos em hospital-escola de instituição pública. J Bras Pneumol, 2002;28(2):71-7.

25. Mendez NH, Moralez DT, Campos JJ, Ortega JM, Vazquez JU, Delgado V, et al. Results of an education program for adult asthmatics [article in Spanish]. Rev Alerg Mex. 2001;48(2):42-4.

26. Lougheed MD, Moosa D, Finlayson S, Hopman WM, Quinn M, Szpiro K, et al. Impact of a provincial asthma guidelines continuing medical education project: The Ontario Asthma Plan of Action's Provider Education I Asthma Care Project. Can Respir J. 2007;14(2):111-7.

27. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o Manejo da Asma 2012. J Bras Pneumol. 2012;38(Suppl 1) S1-S46.

28. Brasil. Ministério da Saúde. Portaria no 2.982, de 26 de Novembro de 2009. Aprova as normas de execução e de financiamento da Assistência Farmacêutica na Atenção Básica. Brasília: Diário Oficial da União, 1 dez 2009; no 229, Sec 1:120.

29. Brasil. Ministério da Saúde. Portaria no 2.981, de 26 de Novembro de 2009. Aprova o Componente Especializado da Assistência Farmacêutica. Diário Oficial da União, 1 dez 2009; no 229, Sec 1:71.

30. Ponte EV, Franco RA, Souza Machado A, Souza Machado C, Cruz AA. Impacto de um programa para o controle da asma grave na utilização de recursos do Sistema Único de Saúde. J Bras Pneumol. 2007;33(1):15-9. http://dx.doi.org/10.1590/S1806-37132007000100006

31. Lasmar L, Fontes MJ, Mohallen MT, Fonseca AC, Camargos P. Wheezy child program: the experience of the belo horizonte pediatric asthma management program. World Allergy Organ J. 2009;2(12):289-95. http://dx.doi.org/10.1097/WOX.0b013e3181c6c8cb

32. Cruz AA, Souza-Machado A, Franco RA, Souza-Machado C, Ponte EV, Santos PM, et al. The impact of a program for control of asthma in a low-income setting. World Allergy Organ J. 2010;3(4):167-74. http://dx.doi.org/10.1097/WOX.0b013e3181dc3383

33. Andrade WC, Camargos P, Lasmar L, Bousquet J. A pediatric asthma management program in a low-income setting resulting in reduced use of health service for acute asthma. Allergy. 2010;65(11):1472-7. http://dx.doi.org/10.1111/j.1398-9995.2010.02405.x

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Original Article

Negative impact of asthma on patients in different age groups*

Impacto negativo da asma em diferentes faixas etárias

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Abstract

Objective: To evaluate the impact of asthma on patients in Brazil, by age group (12-17 years, 18-40 years, and ≥ 41 years). **Methods:** From a survey conducted in Latin America in 2011, we obtained data on 400 patients diagnosed with asthma and residing in one of four Brazilian state capitals (São Paulo, Rio de Janeiro, Curitiba, and Salvador). The data had been collected using a standardized questionnaire in face-to-face interviews. For the patients who were minors, the parents/guardians had completed the questionnaire. The questions addressed asthma control, number of hospitalizations, number of emergency room visits, and school/work absenteeism, as well as the impact of asthma on the quality of life, sleep, and leisure. We stratified the data by the selected age groups. **Results:** The proportions of patients who responded in the affirmative to the following questions were significantly higher in the 12- to 17-year age group than in the other two groups: "Have you had at least one episode of severe asthma that prevented you from playing/exercising in the last 12 months?" (p = 0.012); "Have you been absent from school/work in the last 12 months?" (p < 0.001); "Have you discontinued your asthma relief or control medication in the last 12 months?" (p = 0.008). In addition, 30.2% of the patients in the 12- to 17-year age group reported that normal physical exertion was very limiting (p = 0.010 vs. the other groups), whereas 14% of the patients in the ≥ 41-year age group described social activities as very limiting (p = 0.011 vs. the other groups). **Conclusions:** In this sample, asthma had a greater impact on the patients between 12 and 17 years of age, which might be attributable to poor treatment compliance.

Keywords: Asthma; Age groups; Quality of life.

Resumo

Objetivo: Avaliar o impacto da asma em pacientes segundo as faixas etárias de 12-17 anos, 18-40 anos e ≥ 41 anos no Brasil. **Métodos:** Os dados de 400 pacientes com asma diagnosticada por um médico e residentes de quatro capitais estaduais brasileiras (São Paulo, Rio de Janeiro, Curitiba e Salvador) foram obtidos em um inquérito realizado em países da América Latina em 2011. Os dados foram coletados por meio de um questionário padronizado em entrevista presencial com os pacientes ou com os pais/responsáveis daqueles < 18 anos. As questões abordavam controle da asma, número de hospitalizações, número de consultas de urgência, absenteísmo na escola/trabalho e impactos da asma na qualidade de vida, sono e lazer. Os dados foram estratificados pelas faixas etárias selecionadas. **Resultados:** Em comparação com os grupos de pacientes adultos, houve uma proporção significativamente maior no grupo 12-17 anos em relação a ter ao menos um episódio de asma grave que impediu o paciente a continuar a jogar ou a se exercitar nos últimos 12 meses (p = 0,012), absenteísmo escolar/trabalho nos últimos 12 meses (p < 0,001), e interrupção de medicação para controle ou prevenção da asma nos últimos 12 meses (p = 0,008). Além disso, 30,2% dos pacientes na faixa etária 12-17 anos relataram que esforços físicos normais eram atividades muito limitantes (p = 0,010 vs. outros grupos), enquanto 14% dos pacientes do grupo ≥ 41 anos descreveram as atividades sociais como muito limitantes (p = 0,011 vs. outros grupos). **Conclusões:** Nessa amostra, o impacto da asma foi maior nos pacientes com idade entre 12 e 17 anos do que nos adultos, e isso pode ser atribuído à baixa aderência ao tratamento.

Descritores: Asma; Grupos etários; Qualidade de vida.

Introduction

According to the World Health Organization, an estimated 235 million people worldwide have asthma.[1] In Brazil, the prevalence of clinically diagnosed asthma is approximately 20%, and the frequency of active disease is 10%, rates that are not very different from those found in developed countries.[2] Asthma has a major impact on public and private health care systems in Brazil.

Asthma is one of the leading chronic diseases of childhood and is considered the most prevalent chronic respiratory disease in children and adolescents. It is a potentially serious condition, the prevalence of which has increased worldwide.[3] It affects not only children but also adults, being a global health problem. Fortunately, hospitalization rates for asthma in individuals over 20 years of age decreased by 49% between 2000 and 2010. In 2011, the Brazilian Unified Health Care System Department of Information Technology recorded 160,000 hospitalizations among patients of all ages, asthma being therefore the fourth leading cause of hospitalizations.[4] Factors associated with an increased risk of symptom persistence into adulthood include disease severity, atopy, smoking, and being female.[5]

Because asthma is a chronic disease, patients must adhere to medication and guidelines for the self-management of asthma, which include general information on asthma, written action plans for asthma, and asthma symptom diaries. All of the above are very effective in reducing morbidity and mortality in asthma patients.[6]

The Global Initiative for Asthma classifies asthma patients as having controlled, partly controlled, or uncontrolled asthma on the basis of symptoms, limitations in activities of daily living, nocturnal awakenings, rescue medication use, and pulmonary function data; in addition, it states the importance of achieving and maintaining clinical control of asthma as a treatment goal.[1,7,8] To that end, it is necessary to know the extent to which each goal is met; to identify barriers to asthma control; and to determine whether subgroups of patients stratified by age are at an increased risk because of poor disease control.[1]

This knowledge would allow us to determine the impact of asthma on the quality of life of patients in different age groups and provide appropriate guidance to each group. Our hypothesis was that the level of asthma control was higher in patients between 12 and 17 years of age because they are cared for and supervised by their parents/caregivers. The objective of the present study was to evaluate the impact of asthma on the quality of life of 400 asthma patients residing in one of four Brazilian state capitals, interviewed in person, and stratified by age group (12-17 years, 18-40 years, and ≥ 41 years).

Methods

The Latin America Asthma Insight and Management (LA AIM) survey was conducted in 2011 in Argentina, Brazil, Mexico, Venezuela, and Puerto Rico in order to explore and document patient perception of asthma, as well as patient knowledge of the disease and its forms of treatment.[9] The present study is a cross-sectional study using a subsample of the multicenter LA AIM survey and focusing exclusively on the patients residing in Brazil. The present study was approved by the Research Ethics Committee of the Federal University of São Paulo *Hospital São Paulo* (Ruling no. 250.155).

Initially, 4,545 households in four Brazilian cities (São Paulo, Rio de Janeiro, Curitiba, and Salvador) were selected from a national probability sample. If there were two or more individuals with asthma in the household, one of them was randomly selected. All of the individuals who reported having physician-diagnosed asthma were included. A home visit was scheduled over the telephone, and individuals were interviewed by a professional interviewer trained to administer the questionnaire. A total of 400 individuals were interviewed in person; those who were ≥ 18 years of age were interviewed directly, as were the parents/guardians of those who were between 12 and 17 years of age. The interviews lasted approximately 35 minutes. The questionnaire consisted of 53 questions addressing five major asthma domains: symptoms; impact of asthma on life; perception of asthma control; exacerbations; and treatment/medication.[10]

In order to evaluate the impact of asthma on the daily life of respondents, the questions addressed the frequency of school or work absences due to asthma, activity limitations because of the disease, productivity levels on days when experiencing an asthma attack, and the influence of asthma on the quality of life. Respondents were also asked whether they or their children

had been hospitalized or had been admitted to the ICU in the last 12 months and, if so, how many times. In addition, respondents were asked whether they had sought a physician for exacerbations, symptoms of worsening disease, and severe asthma attacks in the previous year. Respondents also answered questions regarding their (or their children's) treatment.

In the statistical analysis, categorical variables are presented as absolute numbers and percentages, and continuous variables are presented as mean and standard deviation. The chi-square test was used in order to compare categorical variables among the age groups studied (12-17 years, 18-40 years, and ≥ 41 years), and the level of significance was set at $p < 0.05$. Data analysis was performed with the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

We evaluated 400 asthma patients residing in one of four cities in Brazil: São Paulo (47.8%); Rio de Janeiro (36.0%); Curitiba (7.0%); and Salvador (9.2%). Of the 400 patients, 128 (32%) were male and 272 (68%) were female. Most of the patients ≥ 41 years of age were female (p = 0.011). Of the sample as a whole, approximately half had pets in the household (p = 0.037). There were no significant differences among the three age groups regarding the presence of smokers in the household or a history of rhinitis or allergy (Table 1).

Regarding activities of daily living, the proportion of patients who had had at least one episode of severe asthma that prevented them from playing/exercising in the last 12 months was significantly higher in the 12- to 17-year age group than in the other two groups. Of the asthma patients in the 12- to 17-year age group, 67.4% had been absent from school or work in the last 12 months (p < 0.001). There were no significant differences among the groups regarding the other activities of daily living (Table 2).

Regarding activities limited by asthma (Table 3) in the 12- to 17-year age group (n = 43), 13 (30.2%) reported that normal physical exertion was limiting (p = 0.010), whereas 24 (14.0%) of the patients in the ≥ 41-year age group (n = 172) described social and daily activities as limiting (p = 0.011 and p = 0.005, respectively).

There were no differences among the groups regarding episodes of asthma requiring hospitalization or emergency room visit (Table 4).

Of the patients in the 12- to 17-year age group, 48.8% had discontinued their asthma relief or control medication in the last 12 months (p = 0.008; Table 5).

Discussion

The present study evaluated the impact of asthma on patients in three different age groups and showed that the disease had a greater impact on the patients between 12 and 17 years of age than on the adult patients. This finding was inconsistent with our hypothesis that the level of asthma control was higher in patients in the 12- to 17-year age group because they were cared for and supervised by their parents/caregivers.

In our study, we found no significant differences among the age groups regarding the proportions of patients reporting the need for hospitalization, emergency room visits, or urgent physician visits for asthma; however, the proportions were high in the three age groups, ranging from 46.5% to 51.2% (Table 4). A multicenter prospective observational study involving a large cohort of asthma patients was conducted in the USA with the objective of gaining a better understanding of the natural history of asthma in patients with severe or difficult-to-treat asthma.[11] The study found at least one hospitalization or emergency room visit in 5-15% of the adults, in 10-17% of the adolescents, and in 9-22% of the children,[11] a finding that is inconsistent with those of the present study. This shows that the level of asthma control is low among asthma patients in Brazil.[10]

Of the asthma patients in the 12- to 17-year age group in the present study, 67.4% had been absent from school or work in the last 12 months (p < 0.001). Another survey of asthma patients in Latin America[12] sought to assess the quality of asthma treatment and control in Latin America; to determine how closely asthma management guidelines were being followed; and to assess patient perception of, knowledge of, and attitudes toward asthma. In that survey, 79% of the adults and 68% of the children reported that asthma symptoms limited their activities of daily living; in addition, 58% of the children and 31% of the adults reported being absent from school or work because of asthma.[12]

Table 1 – Demographic and clinical characteristics of 400 asthma patients interviewed in one of four Brazilian state capitals and stratified by age group.[a]

Variable	Age group, years			p*
	12-17	18-40	≥ 41	
	(n = 43)	(n = 185)	(n = 172)	
Gender				
Female	20 (46.5)	126 (68.1)	121 (70.3)	0.011
Male	23 (53.5)	59 (31.9)	51 (29.7)	
Pets in the household	24 (55.8)	86 (46.5)	89 (52.0)	0.037
Smokers in the household	24 (55.8)	80 (43.2)	68 (39.5)	0.155
History of rhinitis or allergy	33 (76.7)	143 (77.3)	127 (73.8)	0.738
Level of asthma control[b]				
Controlled	3 (7.0)	24 (13.0)	10 (5.8)	0.197
Partly controlled	26 (60.5)	98 (53.0)	102 (59.3)	
Uncontrolled	14 (32.6)	63 (34.1)	60 (34.9)	

[a]Values expressed as n (%). [b]In accordance with the Global Initiative for Asthma criteria.[7] *Chi-square test.

Table 2 – Activities of daily living affected by asthma in 400 asthma patients interviewed in one of four Brazilian state capitals and stratified by age group.[a]

Variable	Age group, years			p*
	12-17	18-40	≥ 41	
	(n = 43)	(n = 185)	(n = 172)	
Episode of severe asthma that prevented the patient from playing or exercising	23 (53.5)	76 (41.1)	52 (30.2)	0.012
Episode of severe asthma that forced the patient to leave school or work	24 (55.8)	93 (50.3)	63 (36.6)	0.104
School or work absenteeism	29 (67.4)	75 (40.5)	48 (27.9)	< 0.001

[a]Values expressed as n (%). *Chi-square test.

Table 3 – Activities of daily living limited by asthma in 400 asthma patients interviewed in one of four Brazilian state capitals and stratified by age group.[a]

Variable	Age group, years			p*
	12-17	18-40	≥ 41	
	(n = 43)	(n = 185)	(n = 172)	
Sports and recreation	12 (28.0)	24 (13.0)	34 (19.8)	0.197
Normal physical exertion	13 (30.2)	23 (12.5)	42 (24.5)	0.010
Social activities	5 (11.6)	10 (5.5)	24 (14.0)	0.011
Sleep	14 (32.6)	46 (24.9)	49 (28.5)	0.220
Daily activities	7 (16.3)	21 (11.4)	35 (20.3)	0.005

[a]Values expressed as n (%). *Chi-square test.

A study conducted in California, USA, showed that school-age children (4-17 years of age) with daily or weekly asthma symptoms had a higher rate of missing at least one week of school in the last 12 months because of asthma (28%) than did children who experienced asthma symptoms less than once a month (15%). In adults with asthma, the rate of missing at least one week of work in the previous year because of asthma was more than twice as high among those with daily or weekly symptoms (12%) than among those who experienced symptoms less than once a month (5%).[13]

Work absenteeism reduces productivity and, consequently, increases the indirect costs of asthma. A study conducted in France and Spain with the objective of describing costs and quality of life in adult patients with asthma according to the level of asthma control found that patients with uncontrolled asthma increase asthma-related costs in the two countries.[8]

Table 4 – Episodes of asthma requiring hospital admission, ICU admission, unscheduled urgent visit, or emergency room visit in 400 asthma patients interviewed in one of four Brazilian state capitals and stratified by age group.[a]

Variable	Age group, years			p*
	12-17	18-40	≥ 41	
	(n = 43)	(n = 185)	(n = 172)	
Episode of severe asthma requiring hospital admission	28 (65.1)	115 (62.2)	85 (49.4)	0.071
Episode of severe asthma requiring ICU admission	2 (4.7)	11 (5.9)	13 (7.6)	0.914
Emergency visit to a physician's office, a hospital, or a clinic	22 (51.2)	86 (46.5)	79 (45.9)	0.824
Emergency room visits or hospitalizations	13 (30.2)	56 (30.3)	40 (23.3)	0.297
Most commonly used health service				
Private	6 (14.0)	15 (8.1)	20 (11.6)	0.197
Health insurance	15 (34.8)	56 (30.3)	36 (20.9)	
PCC	11 (25.6)	77 (41.6)	83 (48.3)	
Other	11 (25.6)	37 (20.0)	33 (19.2)	

PCC: primary care clinic. [a]Values expressed as n (%). *Chi-square test.

Table 5 – Questions regarding treatment in 400 asthma patients interviewed in one of four Brazilian state capitals and stratified by age group.[a]

Variable	Age group, years			p*
	12-17	18-40	≥ 41	
	(n = 43)	(n = 185)	(n = 172)	
Had heard of peak flow meters	22 (51.2)	64 (34.6)	66 (38.4)	0.334
Owned a peak flow meter	4 (9.3)	4 (2.1)	8 (4.6)	0.248
Had a written action plan for asthma management	19 (44.2)	75 (40.5)	74 (43.0)	0.210
Had used asthma relief or control medication in the last 4 weeks	12 (27.9)	42 (22.7)	50 (29.1)	0.496
Had discontinued asthma relief or control medication in the last 12 months	21 (48.8)	70 (37.8)	55 (31.9)	0.008

[a]Values expressed as n (%). *Chi-square test.

Given that asthma is a chronic disease, long-term treatment adherence is expected. Drug therapy is more effective when patients use corticosteroids regularly. However, many patients refuse to undergo long-term treatment. In addition, it is important to educate patients regarding the use of action plans and PEF diaries. This helps to reduce morbidity and mortality.[14-16]

In our study, there were no differences among the groups regarding the use of asthma relief or control medication (p = 0.496). However, 48.8% of the participants between 12 and 17 years of age had discontinued their asthma relief or control medication in the last 12 months (p = 0.008). There were no differences among the three groups of patients regarding their knowledge of the peak flow meter: approximately half of the patients knew what a peak flow meter was, but only less than 5% had one. In addition, 40% of the patients had received a written treatment

plan, although, ideally, all should have. In a study conducted in India with the objective of investigating self-management in asthma patients, it was found that not all patients had metered dose inhalers at home, and only 2% had a peak flow meter and kept a PEF diary. In addition, none of the patients had received a written treatment plan from their physicians.[6]

In a study conducted in Michigan, USA, with the objective of evaluating adherence to treatment with inhaled corticosteroids in adult asthma patients (in the 18-50 year age bracket), adherence to treatment was found to be poor, being associated with a worse prognosis.[17]

It is known that adherence to inhaled corticosteroids is inadequate in Brazil and other countries.[18-20] In a study conducted in the city of Belo Horizonte, Brazil, with the objective of evaluating the association between adherence to beclomethasone and the level of asthma control in

children between 3 and 12 years of age, adherence to treatment was found to be very low, being a cause for concern.[21] This finding is inconsistent with our hypothesis that the level of asthma control was higher in patients between 12 and 17 years of age because they are presumably cared for and supervised by their parents/caregivers.

Our study has some limitations. Although we included patients residing in one four major cities in Brazil, it is possible that the study population does not represent the population with asthma in Brazil. However, it is unlikely that studies with this type of design can cover the entire population of a country. In addition, the data used in the present study were obtained from self-reports rather than medical records. Another limitation is the fact that parents/guardians completed the questionnaires for the participants between 12 and 17 years of age, which could have introduced an information bias.

In the present study, we found that asthma had a greater impact on the patients between 12 and 17 years of age than on the adult patients. Therefore, we believe that young patients require appropriate counseling for a better understanding of their disease and the importance of adherence to treatment for asthma control. We also believe that programs for parents/caregivers should be developed so that these individuals can counsel their children on the importance of medication use. The opportunity to psychotherapy should also be provided to young patients in order to improve their treatment adherence and quality of life.

In conclusion, asthma has a greater impact on young patients (between 12 and 17 years of age) than on adults, which might be attributable to poor treatment adherence. This shows that a more specific approach is required in order to improve treatment adherence among young patients. The negative impact of asthma on such patients includes lower participation in sports, physical activity, social activities, and daily activities, as well as school/work absenteeism. It is of note that, in the present study, the youngest group had the most contact with domestic animals, which can be a cause of poorer asthma control.

References

1. Chipps BE, Zeiger RS, Dorenbaum A, Borish L, Wenzel SE, Miller DP, et al. Assessment of asthma control and asthma exacerbations in the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) observational cohort. Curr Respir Care Rep. 2012;1(4):259-69. http://dx.doi.org/10.1007/s13665-012-0025-x

2. Stein RT. Pediatric asthma--the impact of hospital admissions. J Bras Pneumol. 2006;32(5):xxv-xxvi. http://dx.doi.org/10.1590/S1806-37132006000500002

3. Maia JG, Marcopito LF, Amaral AN, Tavares Bde F, Santos FA. Prevalence of asthma and asthma symptoms among 13 and 14-year-old schoolchildren, Brazil. Rev Saude Publica. 2004;38(2):292-9. http://dx.doi.org/10.1590/S0034-89102004000200020

4. Ministério da Saúde do Brasil. Departamento de Informática do SUS [homepage on the Internet]. Brasília: DATASUS [cited 2013 May 25]. Morbidade hospitalar do SUS – por local de internação – Brasil. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/miuf.def

5. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma 2012. J Bras Pneumol. 2012;38(Suppl 1) S1-S46.

6. Kotwani A, Shendge S. Asthma self-management: a study in an emergency room of a chest hospital in Delhi, India. South Med Rev. 2012;5(2):20-5. PMid:23532570

7. Global Initiative for Asthma [homepage on the Internet]. Bethesda: NHLBI/WHO [update Dec 2011; cited 2013 May 18.]; 2011. Available from: www.ginasthma.com

8. Doz M, Chouaid C, Com-Ruelle L, Calvo E, Brosa M, Robert J, et al. The association between asthma control, health care costs, and quality of life in France and Spain. BMC Pulm Med. 2013;13:15. http://dx.doi.org/10.1186/1471-2466-13-15

9. Maspero JF, Jardim JR, Aranda A, Tassinari C P, Gonzalez-Diaz SN, Sansores RH, et al. Insights, attitudes, and perceptions about asthma and its treatment: findings from a multinational survey of patients from Latin America. World Allergy Organ J. 2013;6(1):19.

10. Gazzotti MR, Nascimento OA, Montealegre F, Fish J, Jardim JR. Level of asthma control and its impact on activities of daily living in asthma patients in Brazil.J Bras Pneumol. 2013;39(5):532-8. http://dx.doi.org/10.1590/S1806-37132013000500002

11. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al. Design and baseline characteristics of The epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol. 2004;92(1):32-9. http://dx.doi.org/10.1016/S1081-1206(10)61707-3

12. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) survey. Rev Panam Salud Publica. 2005;17(3):191-7. http://dx.doi.org/10.1590/S1020-49892005000300007

13. Meng YY, Babey SH, Hastert TA, Lombardi C, Brown ER. Uncontrolled asthma means missed work and school, emergency department visits for many Californians. Policy Brief UCLA Cent Health Policy Res. 2008;(PB2008-2):1-8.

14. Suissa S, Ernst P, Benayoun S, Baltazan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000;343(5):332-6. http://dx.doi.org/10.1056/NEJM200008033430504

15. Horne R. Compliance, adherence and concordance: implication for asthma treatment. Chest. 2006;130(1 Suppl):65S-72S. http://dx.doi.org/10.1378/chest.130.1_suppl.65S

16. Gibson PG, Powell H, Coughlan J, Wilson A, Abramson MJ, Haywood P, et al. Self-management education and

regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2003;(1):CD001117. PMid:12535399

17. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol. 2004;114(6):1288-93. http://dx.doi.org/10.1016/j.jaci.2004.09.028

18. Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? Ann Allergy Asthma Immunol. 1997;79(3): 177-85; quiz 185-6. http://dx.doi.org/10.1016/S1081-1206(10)63001-3

19. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.

20. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol. 1996;98(6 Pt 1):1051-7. http://dx.doi.org/10.1016/S0091-6749(96)80190-4

21. Lasmar L, Camargos P, Champs NS, Fonseca MT, Fontes MJ, Ibiapina C, et al. Adherence rate to inhaled corticosteroids and their impact on asthma control. Allergy. 2009;64(5):784-9. http://dx.doi.org/10.1111/j.1398-9995.2008.01877.x

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Original Article

Endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer staging: early experience in Brazil*,**

Punção aspirativa por agulha guiada por ultrassom endobrônquico no estadiamento do câncer de pulmão: experiência inicial no Brasil

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Abstract

Objective: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive, safe and accurate method for collecting samples from mediastinal and hilar lymph nodes. This study focused on the initial results obtained with EBUS-TBNA for lung cancer and lymph node staging at three teaching hospitals in Brazil. **Methods:** This was a retrospective analysis of patients diagnosed with lung cancer and submitted to EBUS-TBNA for mediastinal lymph node staging. The EBUS-TBNA procedures, which involved the use of an EBUS scope, an ultrasound processor, and a compatible, disposable 22 G needle, were performed while the patients were under general anesthesia. **Results:** Between January of 2011 and January of 2014, 149 patients underwent EBUS-TBNA for lymph node staging. The mean age was 66 ± 12 years, and 58% were male. A total of 407 lymph nodes were sampled by EBUS-TBNA. The most common types of lung neoplasm were adenocarcinoma (in 67%) and squamous cell carcinoma (in 24%). For lung cancer staging, EBUS-TBNA was found to have a sensitivity of 96%, a specificity of 100%, and a negative predictive value of 85%. **Conclusions:** We found EBUS-TBNA to be a safe and accurate method for lymph node staging in lung cancer patients.

Keywords: Lung neoplasms; Neoplasm staging; Bronchoscopy; Endoscopic ultrasound-guided fine needle aspiration; Lymph nodes.

Resumo

Objetivo: A *endobronchial ultrasound-guided transbronchial needle aspiration* (EBUS-TBNA, punção aspirativa por agulha guiada por ultrassom endobrônquico) é um método seguro e preciso para a coleta de amostras de linfonodos mediastinais e hilares. O presente estudo teve por objetivo avaliar os resultados iniciais com EBUS-TBNA para o estadiamento linfonodal de câncer de pulmão em 3 hospitais acadêmicos no Brasil. **Métodos:** Análise retrospectiva de pacientes com neoplasia de pulmão diagnosticada e submetidos a EBUS-TBNA para estadiamento linfonodal mediastinal. Todos os procedimentos foram realizados sob anestesia geral. Utilizou-se um ecobroncoscópio, uma processadora de ultrassom e agulhas 22 G descartáveis e compatíveis com o ecobroncoscópio. **Resultados:** Entre janeiro de 2011 e janeiro de 2014, 149 pacientes foram submetidos ao estadiamento linfonodal com EBUS-TBNA. A média de idade foi 66 ± 12 anos, sendo 58% do sexo masculino. Um total de 407 linfonodos foram puncionados via EBUS-TBNA. Os tipos mais comuns de neoplasia brônquica foram adenocarcinoma (em 67%) e carcinoma escamoso (em 24%). Para o estadiamento da neoplasia, o EBUS-TBNA apresentou sensibilidade de 96%, especificidade de 100% e valor preditivo negativo de 85%. **Conclusões:** A EBUS-TBNA mostrou-se um método seguro e acurado no estadiamento linfonodal em pacientes com câncer de pulmão.

Descritores: Neoplasias Pulmonares; Estadiamento de neoplasias; Broncoscopia; Aspiração por agulha fina guiada por ultrassom endoscópico; Linfonodos.

Introduction

Lung cancer is the leading cause of cancer death, having accounted for an estimated 160,000 deaths in the United States in 2012.[1] In Brazil, there are approximately 27,000 new cases of lung cancer every year.[2] The prognosis depends on early diagnosis, histology, and staging. The acquisition of CT scans and positron emission tomography/CT (PET/CT) scans represent important steps in the lung cancer staging process. Mediastinal lymph node sampling for cytology and histopathology is essential for accurate staging, because it provides the guidelines for treatment and can avoid unnecessary surgery. Samples for lymph node cytology and histopathology can be obtained endoscopically (by conventional or ultrasound-guided bronchoscopic needle aspiration biopsy) or surgically (by mediastinoscopy, mediastinotomy, mediastinal sampling, or mediastinal lymph node dissection).

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), a minimally invasive method, has been shown to be safe and accurate for collecting samples from mediastinal and hilar lymph nodes. In mediastinal lymph node staging for lung cancer, EBUS-TBNA has been shown to have an accuracy of 98%[3] and has proven to be superior to CT and PET/CT, even in the absence of mediastinal adenopathy (defined as a lymph node diameter ≥ 10 mm) on the CT scan. Because EBUS-TBNA is a nonsurgical procedure, it causes less discomfort to the patient and can be performed on an outpatient basis, resulting in treatment costs that are lower than those associated with mediastinoscopy.[4]

Prospective studies comparing EBUS-TBNA and mediastinoscopy have shown that, in the lymph node staging of non-small cell lung cancer, there is a high level of concordance between the two methods.[4,5] In addition, EBUS-TBNA has the ability to identify contralateral hilar lymph node metastases. This examination begins with the N3 lymph nodes, progressing towards the N2 and N1 lymph node stations. Sampling includes any lymph node station with nodes greater than 5 mm in diameter on their short axis.

Implementing EBUS-TBNA in Brazil has required planning; training of medical and nursing staff; changes to the physical structure of facilities, a new operational protocol; and a billing strategy suited to use of the procedure in Brazil.[6] This study focused on the results obtained with EBUS-TBNA for lung cancer staging at three teaching hospitals in Brazil.

Methods

This was a retrospective cross-sectional study that included patients ≥ 18 years of age diagnosed with lung cancer who underwent EBUS-TBNA for lymph node staging between January of 2011 and January of 2014. The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas*, in the city of São Paulo, Brazil (Protocol no. 435.645).

Every EBUS-TBNA procedure was performed by one of three experienced bronchoscopists, all of whom had been trained in standard and interventional bronchoscopy, with similar levels of training in EBUS-TBNA, each having performed the procedure in more than 50 cases. In all instances, endobronchial ultrasound scope was used (BF-UC180F; Olympus Medical Systems, Tokyo, Japan). Ultrasound imaging was generated by one of two different ultrasound processors—EU-ME1 (Olympus Medical Systems); or Prosound α5 (Aloka, Tokyo, Japan)—and we used a disposable 22 G needle compatible with the ultrasound scope—NA-201SX-4022 (Olympus Medical Systems); ECHO-HD-22-EBUS-O (Cook Medical, Winston-Salem, NC, USA); or GUS-45-18-022 (Medi-Globe, Achenmühle, Germany). The procedure was performed either in the operating room or in the endoscopy suite. In most of the procedures, a trained cytopathologist was present to analyze the lymph node cytological aspirates and determine whether the material collected was satisfactory for diagnosis. The lymph node map reported by Yasufuku et al.[7] was used in order to locate the lymph node stations in all procedures.

As a means of checking the airways for endoluminal lesions, the EBUS-TBNA was preceded by conventional bronchoscopy under local anesthesia (1% xylocaine instilled into the airway). If any such lesions were identified, biopsies were taken only at completion of the EBUS-TBNA staging. The EBUS-TBNA followed standardized steps, from the assessment of CT and PET/CT images to the procedure itself. Planning for the procedure included determining which lymph node stations would be sampled in a sequence of aspiration biopsies, performed initially at the lymph node station farthest from the tumor (N3 station), then moving on to the

lymph node stations closer to the tumor (N2 and N1).[8] The procedure was performed with the patient under general anesthesia, the airway being maintained with a laryngeal mask or endotracheal intubation. Prior to sampling, the mediastinal lymph node stations were mapped, measured, and photographed. The lymph node contents were aspirated in order to collect cell aspirates for cytology, and tissue samples for histology were also collected. The collected material was pushed out from the needle tract by the guidewire onto glass slides or into a container. A single drop of the material was placed on the glass slide and a uniform smear was then produced. The remaining material within the needle tract was flushed out into 10% formaldehyde solution for cell-block preparation. Solid samples were placed into a separate container with 10% formaldehyde solution for histopathology. In the pathology department, fragments and sediment were embedded in paraffin for histology and immunohistochemistry.

The data collected are presented as absolute numbers and percentages. Sensitivity, specificity and negative predictive value for the detection of lymph node metastasis were calculated as follows:

$$sensitivity = tp \ / \ (tp+fn)$$

$$specificity = tn \ / \ (tn+fp)$$
$$positive \ predictive \ value = tp \ / \ (tp+fp)$$
$$negative \ predictive \ value = tn \ / \ (tn+fn)$$

where tp is true positive; tn is true negative; fp is false positive; and fn is false negative. The size difference between malignant and benign lymph nodes was calculated using a z test. The level of significance was set at $p < 0.05$.

Results

One hundred and forty-nine patients diagnosed with lung cancer underwent EBUS-TBNA for lymph node staging. The mean age was 66 ± 12 years, and 87 (58%) of the patients were male. Figure 1 summarizes patient enrollment and the results of the EBUS-TBNA. On the basis of the EBUS-TBNA findings, the cancer was staged as N0/N1 in 69 patients (46%) and as N2/N3 in 80 (54%). The histopathology and mediastinal lymph node staging by EBUS-TBNA are described in Table 1. The tumor histology showed that, in our sample, the most common type of neoplasia was adenocarcinoma, which was identified in 100 cases (67%), followed by squamous cell carcinoma, in 36 (24%), small cell carcinoma, in 7 (5%), carcinoid tumor, in 3 (2%), sarcoma, in 2 (1%) and mucoepidermoid carcinoma, in 1 (0.5%). The EBUS-TBNA identified lung cancer
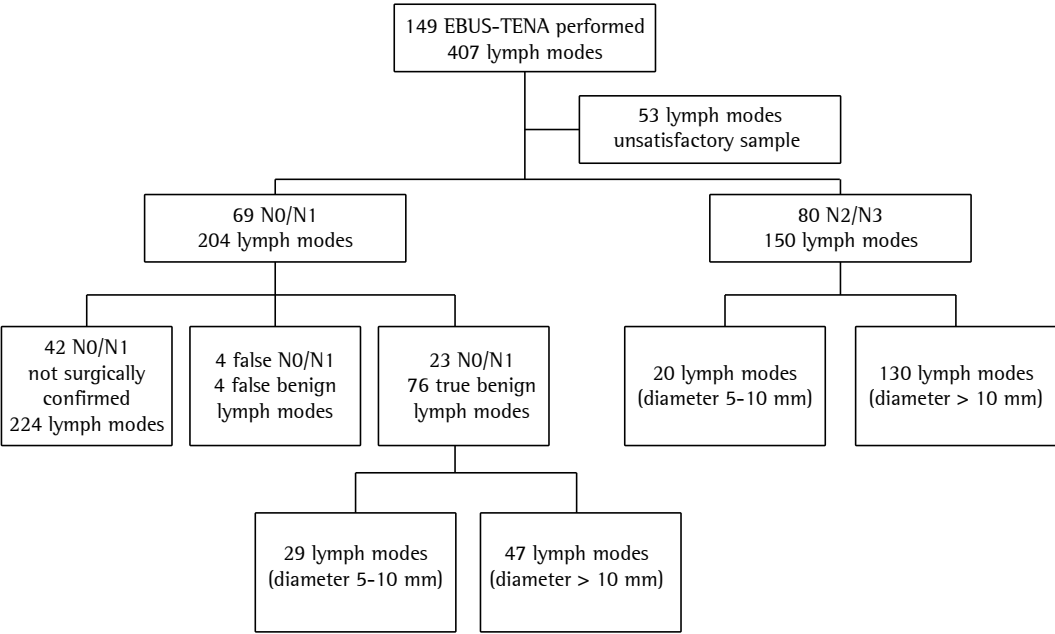
Figure 1 – Flow diagram of patient enrollment, lymph nodes sampled, and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) results.

Table 1 – Histopathology and mediastinal lymph node staging by endobronchial ultrasound-guided transbronchial needle aspiration.

Histopathology	Nº of patients (%)			
	Total	N0/N1	N2	N3
Adenocarcinoma	100 (67)	46 (46)	34 (34)	20 (20)
Squamous cell carcinoma	36 (24)	17 (47)	14 (39)	5 (14)
Small cell carcinoma	7 (5)	1 (14)	5 (72)	1 (14)
Carcinoid tumor	3 (2)	2 (67)	0	1 (33)
Sarcoma	2 (1)	2 (100)	0	0
Mucoepidermoid carcinoma	1 (0,7)	1 (100)	0	0
Total	149 (100)	69 (46)	53 (36)	27 (18)

and N0/N1 lymph nodes in 69 patients, of whom 27 (39%) underwent surgical lymph node staging. There were 23 true-positive results and 4 false-negative results (3 adenocarcinomas and 1 carcinoid tumor). Of the remaining 42 patients (those in whom the staging was not confirmed by surgery), 32% were considered unfit for surgery, 17% had distant metastases, 4% had another primary tumor outside the lung, and 13% were lost to follow up. There was one procedure-related complication—endobronchial bleeding at the puncture site in a patient with small cell carcinoma—which was controlled endoscopically. There was no procedure-related mortality among the patients in our sample.

A total of 407 lymph nodes with a diameter ≥ 5 mm were assessed by EBUS-TBNA, with an average of 3.15 lymph nodes per patient. Fifty-three (13%) of the punctures were considered unsatisfactory for analysis by the pathologist. The lymph node stations sampled were 2R (0.8%); 2L (0.4%); 4R (23.5%); 4L (14.0%); 7 (30.8%); 10R (6.0%); 10L (4.6%); 11R (8.8%); 11L (10.4%); 12R (0.4%); and 12L (0.2%). Cytology and histology samples are depicted in Figures 2 and 3, respectively.

The final cytologic diagnosis and diameter of lymph nodes are described in Table 2. As far as lymph node size is concerned, the comparison between benign and malignant lymph nodes showed that those > 10 mm in diameter were more often malignant. Of the 407 lymph nodes biopsied, 76 (19%) were classified as benign on the basis of the surgical findings. Of those 76 lymph nodes, 47 (62%) had a diameter > 10 mm and 29 (38%) had a diameter of 5-10
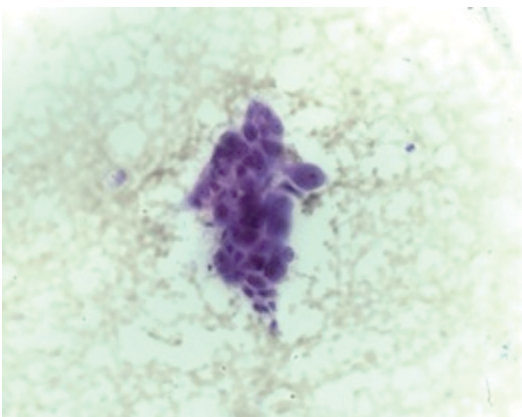
Figure 2 – Fine needle aspiration cytology of a lymph node with squamous carcinoma (thionin staining; magnification, ×400). Courtesy of the Pathology Laboratory, Heart Institute, University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.
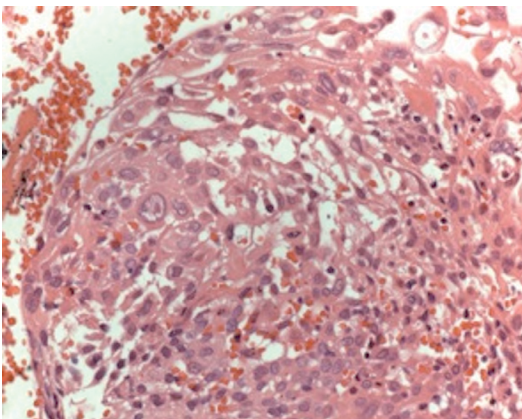
Figure 3 – Cell block histopathology of a lymph node with squamous carcinoma (Hematoxylin-eosin staining; magnification, ×400). Courtesy of the Pathology Laboratory, Heart Institute, University of São Paulo School of Medicine *Hospital das Clínicas*, São Paulo, Brazil.

mm, reactive lymphadenitis being identified in 75 and one testing positive for tuberculosis. The finding of malignancy in lymph nodes that had been classified as unsuspicious by other imaging methods (PET/CT and CT scan) resulted in a change in the management strategy in 5 patients (corresponding to 33% of the patients in whom PET/CT and CT scans had raised no suspicion about the mediastinal lymph nodes in question). Lymph node diameters and final cytologic diagnoses are shown in Table 2. For the detection of lymph node metastasis in our sample, EBUS-TBNA had a sensitivity of 96% (103

Table 2 – Final cytologic diagnosis in 407 lymph nodes.

Final cytologic diagnosis	Nº of lymph nodes (%)		
	n (%)	Diameter	
		5-10 mm	> 10 mm
Positive for malignant cells	150 (37)	20 (13)	130 (87)*
Benign[a]	76 (19)	29 (38)	47 (62)*
Negative for malignant cells[b]	128 (31)	38 (30)	90 (70)
False benign	4 (1)	1 (25)	3 (75)
Unsatisfactory sample	53 (13)	7 (13)	46 (87)
Total	407	91 (22)	316 (78)

*significant difference (p < 0.001; 95% CI: 0.137-0.363).
[a]Confirmed by surgery. [b]Not confirmed by surgery.

of 117), a specificity of 100%, and a negative predictive value of 85% (23 of 27).

Discussion

Preliminary results from the first three centers in Brazil at which it was implemented have demonstrated that the EBUS-TBNA procedure is a safe and accurate method for staging lung cancer. The preference for general anesthesia over conscious sedation is based on the comfort the former provides the patient as well as the EBUS-TBNA team. Performing the cytopathology in the room often adds time to the procedure in exchange for more accurate results. However, the routine use of general anesthesia increases costs and procedural time (in the operating room or endoscopy suite). As far as accuracy is concerned, one study comparing deep and conscious sedation for EBUS-TBNA cancer staging showed that more lymph nodes were sampled under deep sedation than under conscious sedation, the diagnostic yields being 80% and 66%, respectively.[9] Because the EBUS-TBNA procedure is not only technically demanding but also labor-intensive, we believe that either deep sedation or general anesthesia are necessary in order to perform the procedure easily and safely. In addition, instruction in EBUS-TBNA at teaching hospitals is facilitated if the procedure is performed under general anesthesia. At some facilities, EBUS-TBNA is performed with a rigid bronchoscope under general anesthesia.[10] At others, it is performed through an endotracheal tube under deep sedation or through a laryngeal mask under general anesthesia.[11,12] At our facility,

the preference is for performing the procedure through a laryngeal mask under general anesthesia.

Various strategies for approaching mediastinal and hilar lymph nodes have been proposed.[8] Lymph node puncture can be performed concurrently with the lymph node mapping, the lymph nodes with malignant characteristics, such as diameter > 10 mm, spherical shape, well-defined margins, necrosis, heterogeneity, and absence of hilum, being identified selectively.[13] In our study, we elected to do the ultrasound mapping of all accessible lymph nodes prior to the puncture of the lymph node stations. As recommended by other authors,[11,13] we sampled lymph nodes ≥ 5 mm in diameter, which would presumably have a greater impact on staging and management.

We found that, among the lung cancer patients evaluated in the present study, lymph nodes > 10 mm in diameter were more often malignant, as reported in the literature. However, Herth et al.[14] reported that, for the detection of metastatic lymph nodes of 5-10 mm in diameter, EBUS-TBNA has a sensitivity of 89% and a negative predictive value of 98.9%. In our study, 13% of the lymph nodes positive for malignancy were ≤ 10 mm in diameter. That finding resulted in a change in the management of the cancer in 5 patients (33% of the patients in whom mediastinal lymph nodes had been classified as unsuspicious on PET/CT and CT scans). In this context, EBUS-TBNA might play an important role in the approach to mediastinal and hilar lymph nodes initially considered metastatic or nonmetastatic solely on the basis of their diameter, as determined by other imaging methods. Our data show that 62% of the truly benign mediastinal lymph nodes were > 10 mm in diameter, whereas 13% of the true malignant mediastinal lymph nodes were smaller than 10 mm in diameter. Another study comparing CT, PET/CT, and EBUS-TBNA for the detection of lymph node metastasis in a sample of 102 patients with lung cancer showed that the accuracy of CT, PET/CT, and EBUS-TBNA was 60.8%, 72.5%, and 98%, respectively.[3]

In EBUS-TBNA samples, the lymph node morphology can also suggest malignancy. Certain characteristics, such as being round, having heterogeneous density, showing necrosis, and having well-defined margins can be suggestive of malignancy. Conversely, having a diameter < 10 mm, having an oval shape, having homogeneous

density, showing no necrosis, having ill-defined margins and the presence of a central hilar structure are suggestive of a benign lymph node.[13]

The present study has certain limitation. Because of the retrospective design and the small number of patients, we cannot draw any correlations between lymph node ultrasound patterns and the presence of metastasis. Nevertheless, given the high prevalence of infectious granulomatous diseases in our patient population, the recognition and differentiation of lymph node ultrasound patterns might become important for discerning between benign and malignant disease.

We consider the presence of a cytopathologist during the procedure essential to determining whether the material collected is satisfactory (in terms of volume and character) for diagnosis. A cytopathologist can also contribute to the screening and processing of samples for other procedures, such as histochemistry, immunohistochemistry, genetic mutation testing, and culture.[15]

It has been reported that the learning curve for EBUS-TBNA is "steep", the performance of at least 50 procedures, under the supervision of an experienced bronchoscopist, being required in order to train a specialist.[7] In fact, in a preliminary study involving only 50 patients, we found that only 74% of the samples were considered satisfactory for cytology.[16] Since then, that proportion has increased considerably as we have gained expertise and started using on-site cytopathology during the EBUS-TBNA procedures. Other authors have questioned whether it is necessary to have a cytopathologist in the room in order to improve the diagnostic accuracy of EBUS-TBNA.[17] After our initial experience with EBUS-TBNA was reported, improvements were made in the technique, as well as in the collection, preparation, and processing of samples, and team experience was enhanced. Most importantly, the presence of a cytopathologist in the room has reduced the proportion of samples considered unsatisfactory for diagnosis from 26% in the first year of our experience to 13% at this writing.

There is considerable evidence that EBUS-TBNA is a safe procedure, the reported rate of complications—including minor complications such as bronchospasm and endobronchial bleeding, as well as more severe complications, such as pneumomediastinum and mediastinitis—ranging from 0.5% to 1.2%.[18] In the present study, we observed only one procedure-related complication among the 149 patients evaluated, and there were no procedure-related deaths.

New methods aimed at improving EBUS-guided sample collection have been reported.[19] Such methods include the use of mini-forceps for the collection of lymph node fragments through small perforations on the bronchial wall.[19] In addition, analysis of the genetic profile of the tumors in the samples collected has recently been included in EBUS-TBNA protocols.[20,21] Within this context, changes in the procedure, as well as in the collection and analysis of the samples, are indicators of the ongoing technological development of EBUS-TBNA.

In conclusion, the early results obtained with EBUS-TBNA in Brazil indicate that it is a safe and accurate procedure for lung cancer staging. It is a minimally invasive procedure whose results can have a significant impact on the therapeutic strategy, the chance of a patient undergoing unnecessary surgery being higher when treatment decisions are based on radiological findings alone. The success of EBUS-TBNA depends on collaboration among the members of a multidisciplinary team composed of medical (bronchoscopist, cytopathologist and anesthesiologist) and paramedical staff.

References

1. American Lung Association [homepage on the Internet]. Washington DC: The Association [cited 2014 Aug 30]. Lung Cancer Fact Sheet. Available from: http://www.lung.org/lung-disease/lung-cancer/resources/facts-figures/lung-cancer-fact-sheet.html

2. Instituto Nacional de Câncer. [homepage on the Internet]. Rio de Janeiro: Ministério da Saúde do Brasil [cited 2014 Aug 30]. Incidência de Câncer no Brasil: estimativa 2014. Available from: http://www.inca.gov.br/estimativa/2014

3. Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest. 2006;130(3):710-8. http://dx.doi.org/10.1378/chest.130.3.710

4. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg. 2011;142(6):1393-400.e1. http://dx.doi.org/10.1016/j.jtcvs.2011.08.037

5. Ernst A, Anantham D, Eberhardt R, Krasnik M, Herth FJ. Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. J Thorac Oncol. 2008;3(6):577-82. http://dx.doi.org/10.1097/JTO.0b013e3181753b5e

6. Figueiredo VR, Jacomelli M, Rodrigues AJ, Canzian M, Cardoso PF, Jatene FB. Current status and clinical applicability of endobronchial ultrasound-guided transbronchial needle aspiration. J Bras Pneumol. 2013;39(2):226-37. http://dx.doi.org/10.1590/S1806-37132013000200015

7. Endobronchial ultrasound: an atlas and practical guide. Ernst A, Herth FJ, editors. Dordrecht; New York: Springer; 2009. 169 p.

8. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol. 2009;4(5):568-77. http://dx.doi.org/10.1097/JTO.0b013e3181a0d82e

9. Yarmus LB, Akulian JA, Gilbert C, Mathai SC, Sathiyamoorthy S, Sahetya S, et al. Comparison of moderate versus deep sedation for endobronchial ultrasound transbronchial needle aspiration. Ann Am Thorac Soc. 2013;10(2):121-6. http://dx.doi.org/10.1513/AnnalsATS.201209-074OC

10. Nakajima T, Yasufuku K. The techniques of endobronchial ultrasound-guided transbronchial needle aspiration. Innovations (Phila). 2011;6(1):57-64. http://dx.doi.org/10.1097/IMI.0b013e31820c91a7

11. Endobronchial ultrasonography. Kurimoto N, Fielding D, Musani A, editors. Oxford: Wiley-Blackwell; 2011. 176 p. http://dx.doi.org/10.1002/9781444314366

12. Fujiwara T, Yasufuku K, Nakajima T, Chiyo M, Yoshida S, Suzuki M, et al. The utility of sonographic features during endobronchial ultrasound-guided transbronchial needle aspiration for lymph node staging in patients with lung cancer: a standard endobronchial ultrasound image classification system. Chest. 2010;138(3):641-7. http://dx.doi.org/10.1378/chest.09-2006

13. Herth FJ, Eberhardt R, Krasnik M, Ernst A. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. Chest. 2008;133(4):887-91. http://dx.doi.org/10.1378/chest.07-2535

14. Monaco SE, Pantanowitz L, Khalbuss WE. Comparing endobronchial ultrasound-guided fine needle aspiration specimens with and without rapid on-site evaluation. Cytojournal. 2012;9:2. http://dx.doi.org/10.4103/1742-6413.92414

15. Tedde ML, Figueiredo VR, Terra RM, Minamoto H, Jatene FB. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis and staging of mediastinal lymphadenopathy: initial experience in Brazil. J Bras Pneumol. 2012;38(1):33-40. http://dx.doi.org/10.1590/S1806-37132012000100006

16. Griffin AC, Schwartz LE, Baloch ZW. Utility of on-site evaluation of endobronchial ultrasound-guided transbronchial needle aspiration specimens. Cytojournal. 2011;8:20. http://dx.doi.org/10.4103/1742-6413.90081

17. Asano F, Aoe M, Ohsaki Y, Okada Y, Sasada S, Sato S, et al. Complications associated with endobronchial ultrasound-guided transbronchial needle aspiration: a nationwide survey by the Japan Society for Respiratory Endoscopy. Respiratory Res. 2013;14:50. http://dx.doi.org/10.1186/1465-9921-14-50

18. Franke KJ, Bruckner C, Szyrach M, Ruhle KH, Nilius G, Theegarten D. The contribution of endobronchial ultrasound-guided forceps biopsy in the diagnostic workup of unexplained mediastinal and hilar lymphadenopathy. Lung. 2012;190(2):227-32. http://dx.doi.org/10.1007/s00408-011-9341-0

19. Bulman W, Saqi A, Powell CA. Acquisition and processing of endobronchial ultrasound-guided transbronchial needle aspiration specimens in the era of targeted lung cancer chemotherapy. Am J Respir Crit Care Med. 2012;185(6):606-11. http://dx.doi.org/10.1164/rccm.201107-1199CI

20. Santis G, Angell R, Nickless G, Quinn A, Herbert A, Cane P, et al. Screening for EGFR and KRAS mutations in endobronchial ultrasound derived transbronchial needle aspirates in non-small cell lung cancer using COLD-PCR. PLoS One. 2011;6(9):e25191. http://dx.doi.org/10.1371/journal.pone.0025191

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Preoperative predictive factors for intensive care unit admission after pulmonary resection*

Fatores preditivos pré-operatórios de internação em unidade de terapia intensiva após ressecção pulmonar

Liana Pinheiro, Ilka Lopes Santoro, João Aléssio Juliano Perfeito, Meyer Izbicki, Roberta Pulcheri Ramos, Sonia Maria Faresin

Abstract

Objective: To determine whether the use of a set of preoperative variables can predict the need for postoperative ICU admission. **Methods:** This was a prospective observational cohort study of 120 patients undergoing elective pulmonary resection between July of 2009 and April of 2012. Prediction of ICU admission was based on the presence of one or more of the following preoperative characteristics: predicted pneumonectomy; severe/very severe COPD; severe restrictive lung disease; FEV_1 or DLCO predicted to be < 40% postoperatively; SpO_2 on room air at rest < 90%; need for cardiac monitoring as a precautionary measure; or American Society of Anesthesiologists physical status ≥ 3. The gold standard for mandatory admission to the ICU was based on the presence of one or more of the following postoperative characteristics: maintenance of mechanical ventilation or reintubation; acute respiratory failure or need for noninvasive ventilation; hemodynamic instability or shock; intraoperative or immediate postoperative complications (clinical or surgical); or a recommendation by the anesthesiologist or surgeon to continue treatment in the ICU. **Results:** Among the 120 patients evaluated, 24 (20.0%) were predicted to require ICU admission, and ICU admission was considered mandatory in 16 (66.6%) of those 24. In contrast, among the 96 patients for whom ICU admission was not predicted, it was required in 14 (14.5%). The use of the criteria for predicting ICU admission showed good accuracy (81.6%), sensitivity of 53.3%, specificity of 91%, positive predictive value of 66.6%, and negative predictive value of 85.4%. **Conclusions:** The use of preoperative criteria for predicting the need for ICU admission after elective pulmonary resection is feasible and can reduce the number of patients staying in the ICU only for monitoring.

Keywords: Thoracic surgery; Risk factors; Intensive care units.

Resumo

Objetivo: Avaliar se a utilização de um conjunto de variáveis pré-operatórias é capaz de antever a necessidade de internação em UTI no pós-operatório. **Métodos:** Estudo de coorte observacional prospectivo, com 120 pacientes submetidos à ressecção pulmonar eletiva entre julho de 2009 e abril de 2012. A previsão de indicação de internação em UTI indicação foi baseada na presença de uma ou mais das seguintes condições pré-operatórias: previsão de pneumonectomia; DPOC grave/muito grave; doença restritiva grave; VEF_1 ou DLCO previstos para o pós-operatório < 40% do previsto; SpO_2 em repouso e ar ambiente < 90%; necessidade de monitorização cardíaca profilática; classificação da *American Society of Anesthesiologists* ≥ 3. O padrão ouro para internação justificada em UTI foi baseado na presença de uma ou mais das seguintes condições pós-operatórias: manutenção de ventilação mecânica ou reintubação; insuficiência respiratória aguda ou necessidade de ventilação não invasiva; instabilidade hemodinâmica ou choque; intercorrências intraoperatórias ou no pós-operatório imediato (cirúrgicas ou clínicas); indicação do anestesiologista ou cirurgião para a manutenção de tratamento na UTI. **Resultados:** Dos 120 pacientes avaliados, houve previsão de necessidade de internação em UTI em 24 (20,0%), sendo essa considerada justificada em 16 deles (66,6%) desses 24, ao passo que dos 96 pacientes sem previsão de necessidade de internação em UTI, essa foi necessária em 14 (14,5%). A utilização dos critérios preditivos para a internação em UTI mostrou boa acurácia (81,6%), sensibilidade de 53,3%, especificidade de 91%, valor preditivo positivo de 66,6% e valor preditivo negativo de 85,4%. **Conclusões:** A utilização de critérios pré-operatórios para a indicação de internação em UTI após ressecção pulmonar eletiva é factível e é capaz de reduzir o número de pacientes que aí permanecem apenas para vigilância.

Descritores: Cirurgia torácica; Fatores de risco; Unidades de terapia intensiva.

Introduction

According to the 1997 American Thoracic Society[1] statement regarding ICU allocation decisions, the primary goal of the ICU is "to preserve meaningful human life by protecting and sustaining patients in a caring manner when they are threatened by an acute critical illness or injury or as a consequence of medical or surgical therapy". The 1999 update[2] adds that the ICU serves to monitor and care for patients with potentially severe physiological instability requiring technical and/or artificial life support.

The European Respiratory Society and the European Society of Thoracic Surgeons[3] do not recommend systematic ICU admission after thoracotomy. Patients who are estimated to be at low risk for complications should be referred to a dedicated thoracic surgery unit. Patients with reduced cardiopulmonary reserve undergoing complex resection and patients who are estimated to be at moderate to high risk for complications should be referred to a high-dependency unit, if available, whereas patients requiring support for organ failure should be admitted to the ICU.

It is known that among patients admitted to the ICU after surgery, only a minority develops acute complications requiring immediate intervention; the majority is referred to the ICU for "surveillance" of possible deterioration of their clinical condition or simply for monitoring.[4-6] It should be noted that patients referred to the ICU only for monitoring may experience unfavorable outcomes, such as increased stress due to the environment as well as to sleep and family deprivation. In addition, there is a substantial increase in hospital costs.[7]

Thoracic surgery always results in pulmonary dysfunction, and depending on the degree of impairment, there can be difficulty in extubating the patient at the end of the surgical procedure and need for prolonged mechanical ventilation. In addition, many surgical candidates present with comorbidities and/or compromised cardiopulmonary reserve, which makes them more susceptible to developing perioperative complications.[2,3] However, the question regarding the proportion of these patients who would benefit from the ICU setting in the immediate postoperative period also remains unanswered.

Few studies have bothered to determine prognostic factors associated with the need for ICU admission,[8-11] and in the literature there is no consensus regarding indications for ICU admission after pulmonary resection. Therefore, we decided to design a study to investigate whether the use of a set of preoperative variables can predict the need for immediate postoperative ICU admission.

Methods

A prospective observational cohort study of patients referred to the outpatient preoperative evaluation clinic of the Department of Pulmonology of the *Universidade Federal de São Paulo* (UNIFESP, Federal University of São Paulo) was carried out between July of 2009 and April of 2012. This study was approved by the UNIFESP Research Ethics Committee (Ruling no. 410/09).

We included patients over 18 years of age undergoing elective pulmonary resection, with diagnosed or suspected benign or malignant disease. The exclusion criteria were as follows: incomplete preoperative evaluation; one concomitant surgical procedure in addition to pulmonary resection; parenchymal-sparing procedures; and preoperative or intraoperative death.

After giving written informed consent, participants underwent a preoperative evaluation consisting of clinical assessment and physical examination, with the use of a structured form. Pulmonary function was assessed by using the modified algorithm presented in the American College of Chest Physicians (ACCP) guidelines,[12] with the following tests: pre- and post-bronchodilator spirometry; pulse oximetry; DLCO measurement; pH measurement and arterial blood gas analysis; cardiopulmonary exercise testing; and pulmonary perfusion mapping. On completing the evaluation, patients were categorized as being at high or acceptable risk.

All patients were operated on by the same team of thoracic surgeons and were referred to the ICU of the Pulmonology Section in the immediate postoperative period, being subsequently transferred to the thoracic surgery ward. They were prescribed epidural or intravenous analgesia by the pain team and received physiotherapy until they were discharged.

Preoperative variables collected included age, gender, surgical disease diagnosis, proposed surgery, smoking, respiratory symptoms, comorbidities, Charlson comorbidity index,[13] and American Society of Anesthesiologists (ASA) physical status,[14] as well as baseline and predicted postoperative

(ppo) values for FVC, FEV_1, FEV_1/FVC, DLCO, and maximal oxygen uptake.

Intraoperative variables analyzed included anesthesia time, procedure performed, number of segments resected, and surgical and clinical complications.

Postoperative variables analyzed included pulmonary complications (prolonged mechanical ventilation, acute respiratory failure [ARF], pulmonary infection, atelectasis, bronchospasm, and oxygen therapy at discharge); hemodynamic complications (shock, hypotension, cardiac arrhythmia, heart failure, and hypertensive crisis); and surgical complications (bronchial fistula, air leak for more than seven days, bleeding requiring transfusion or reoperation, pneumothorax, and empyema; Chart 1).[15-18]

Prediction of the need for ICU admission was based on the presence of one or more of the following preoperative characteristics: planned pneumonectomy; severe/very severe COPD (FEV_1/FVC < 0.7 and FEV_1 < 50% predicted); severe restrictive lung disease (FVC < 50% predicted); ppo-FEV_1 or ppo-DLCO < 40%; SpO_2 on room air at rest < 90%; need for cardiac monitoring as a precautionary measure; or ASA physical status $\geq$ 3.

The gold standard for mandatory admission to the ICU was based on the presence of one or more of the following postoperative characteristics: need for maintenance of invasive mechanical ventilation after surgery or for reintubation; ARF or need for noninvasive positive pressure ventilation; hypotension with hemodynamic instability or associated with signs of shock, requiring blood transfusion as well as fluid resuscitation; unresolved intraoperative or immediate postoperative complications (clinical or surgical); or a recommendation by the anesthesiologist or surgeon to continue treatment in the ICU.

Statistical analysis

Categorical variables were summarized as absolute and relative frequencies (percentages). Numerical variable data were expressed as mean, standard deviation, median, and interquartile range. Diagnostic performance of the ICU admission prediction model was tested by calculating sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, and was measured against the gold standard for mandatory ICU admission. All data were tabulated using Microsoft® Excel 2007. For statistical calculations, we used the Statistical Package for the Social Sciences for Windows, version 19.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA).

Results

Figure 1 depicts the flowchart of patient selection. The clinical and functional characteristics

Chart 1 – Criteria for the diagnosis of complications observed after pulmonary resection.[15-18]

Complication	Criteria
PMV	Need for mechanical ventilation for more than 48 hours after surgery for treatment of ARF.[15]
Pulmonary infection	Antimicrobial treatment for suspected pulmonary infection, associated with at least one of the following criteria: onset of purulent secretions or change in character of secretions; presence of a new opacity on chest X-ray or progression of a pre-existing one; fever; or leukocytosis > 12,000 cells/mm³.[15,16]
Atelectasis	Chest X-ray findings consistent with onset or worsening of respiratory symptoms.
Bronchospasm	Wheezing on lung auscultation associated with shortness of breath and requiring medications, as long as LHF and PTE are ruled out.
ARF	Clinical condition resulting from acutely impaired gas exchange and requiring invasive ventilatory support.
Shock	Absolute hypotension (systolic blood pressure less than 90 mmHg) or relative hypotension (a greater than 40 mmHg decrease in systolic blood pressure) associated with signs of hypoperfusion, oliguria, pallor, cold skin, altered mental status, and metabolic acidosis, with hemodynamic instability or requiring vasoactive medication.[17]
Hypotension	Hypotension requiring fluid resuscitation and blood transfusion.
Oxygen therapy	Need for home oxygen therapy after hospital discharge.[18]

PMV: prolonged mechanical ventilation; ARF: acute respiratory failure; LHF: left heart failure, and PTE: pulmonary thromboembolism.

of the 120 patients included in the study are shown in Table 1.

DLCO was measured in 31 patients (25.8%), and its mean ± SD was 64.4 ± 19% predicted. Maximal oxygen consumption was determined in 4 patients who underwent cardiopulmonary exercise testing, and its mean was 21 mL • kg^{-1} • min^{-1} or 74.5% predicted.

The mean anesthesia time was 6.1 ± 1.8 hours. The surgical procedures performed
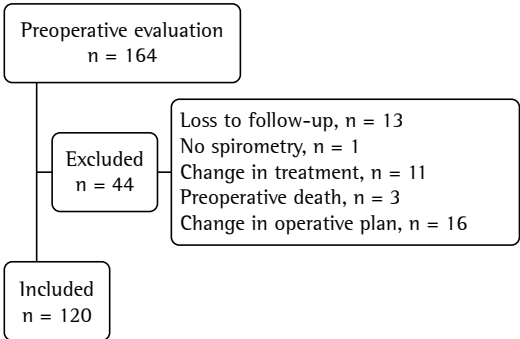
Figure 1– Flowchart of patient selection.

Table 1 – Clinical, functional, and histopathological characteristics of the 120 patients undergoing pulmonary resection.[a]

Characteristic	Result
Male gender	65 (54.2)
Age (years)	56.2 ± 12.3
Number of respiratory symptoms[b]	2 (0-3)
Number of comorbidities[b]	2 (1-3)
Charlson index[b]	3 (2-4)
Smoker	75 (62.5)
ASA physical status	
1	4 (3.3)
2	111 (92.5)
3	5 (4.2)
Functional parameter	
FVC	88.4 ± 17.6
FEV$_1$	82.3 ± 19.2
FEV$_1$/FVC	0.75 ± 0.1
ppo-FEV$_1$	72.4 ± 19.3
DLCO	64.4 ± 19.0
ppo-DLCO	53.4 ± 15.2
Histopathological diagnosis	
Benign disease	41 (34.2)
Malignant disease	79 (65.8)
Primary lung cancer	52 (43.3)
Metastatic cancer	27 (22.5)

ASA: American Society of Anesthesiologists; and ppo: predicted postoperative. [a]Values expressed as n (%) or as mean ± SD, except where otherwise indicated. [b]Values expressed as median (interquartile range).

were pneumonectomy (in 16 patients; 13.4%); lobectomy (in 58; 48.3%); bilobectomy (in 1; 0.8%); trisegmentectomy (in 2; 1.6%); segmentectomy (in 16; 13.4%); and other minor operations (in 27; 22.5%).

Pathological examination of the surgical specimens revealed benign disease in 41 patients (34.1%) and malignant disease in 79 (65.9 %; Table 1).

Thirty-nine patients (32.5%) had a total of 89 complications. Of those, 64 (72%) were clinical complications and 25 (28%) were surgical complications. Hypotension requiring fluid resuscitation and blood transfusion or shock of various etiologies was the most common clinical complication (21; 23.7%), followed by pulmonary infection (15; 16.9%), ARF and/or need for mechanical ventilation after surgery (10; 11.2%), arrhythmia (7; 7.9%), and bronchospasm (3; 3.4%). There were two episodes (2.2%) of each of the following complications: atelectasis; acute pulmonary edema; need for oxygen therapy at hospital discharge; and hypertensive crisis. Bleeding was the most common surgical complication (11; 12.3%), followed by bronchial fistula (5; 5.6%), empyema (4; 4.5%), prolonged air leak (3; 3.4%), and pneumothorax (2; 2.2%).

The 30-day mortality rate was 2.5% (3/120), and three deaths were due to septic shock from pulmonary infection, which, in 2 cases, was preceded by a bronchial fistula. The 3 patients in question had a diagnosis of bronchiectasis with aspergilloma. Another 4 deaths occurred after 30 days, but during the same hospital stay: 2 occurred during an operation for bronchiectasis and 2 occurred during an operation for cancer.

Among the 120 patients evaluated, 24 (20.0%) were predicted to require ICU admission, and the clinical criteria for this prediction are shown in Table 2.

Among those 24 cases, there were 16 true positives and 8 false positives. Of those 8 false positives, 1 underwent surgical treatment of bleeding bronchiectasis, had restrictive lung disease, and had a ppo-DLCO of 33%, and 1 had severe COPD, with a preoperative FEV$_1$ of 45% predicted and an SpO$_2$ of 88%. In the remaining 6, the proposed surgical procedure was pneumonectomy. All false positives were discharged from the ICU in the morning after the procedure (Table 3).

Among the 96 patients for whom ICU admission was not predicted, there were 96 true negatives and 14 false negatives. Those 14 false negatives were ASA physical status 2, had a mean age of 60 years, and had a mean ppo-FEV$_1$ of 70%; in addition, the proposed surgical procedure was not pneumonectomy (Table 3).

The accuracy of the ICU admission prediction model was 81.6% (98/120), with sensitivity of 53.3%, specificity of 91%, positive predictive value of 66.6%, and negative predictive value of 85.4%.

Analysis of the false negative subgroup revealed that, in 2 cases, the operation was converted from lobectomy to pneumonectomy intraoperatively; 2 patients developed arrhythmia, which was promptly corrected, and 12 patients had shock or hypotension requiring transfusion, the shock being caused by intraoperative or immediate postoperative bleeding in 10 (Table 4).

Discussion

Studies on criteria for predicting ICU admission after pulmonary resection are few in number and have included mainly patients with lung cancer. [7,10,11] When planning this study, we decided to include patients with benign diseases as well, because, in developing countries, surgical procedures for the treatment of bronchiectasis and other post-infectious pulmonary sequelae are still very common. Benign diseases are known to be more prevalent in patients younger than those presenting with cancer, but this does not make the rates of postoperative morbidity (18 to 46%) and mortality (zero to 26.3%) any lower. [19-21]

In 2008, Brunelli et al. [10] developed and validated the first risk scale for predicting the need for ICU admission after pulmonary resection, principally for patients with lung cancer. Of the 1,297 participants, 82 (6.3%) required ICU admission, and, using the logistic regression model, those authors found that the independent predictors of need for ICU admission were age over 65 years, ppo-FEV$_1$ < 65%, ppo-DLCO < 50%, cardiac comorbidities, and pneumonectomy.

Okiror et al. [11] performed external validation of the scale developed in aforementioned study and concluded that the scale of Brunelli et al. had a moderate discriminatory power for predicting the need for ICU admission. However, the criteria used in the validation study were not the same as those of the original study (emergency ICU

Table 2 – Factors for predicting the need for ICU admission in 24 patients undergoing pulmonary resection.

Reason	n (%)
Pneumonectomy	13 (10.8)
ASA physical status 3	5 (4.2)
Severe COPD	3 (2.5)
ppo-FEV$_1$ or ppo-DLCO < 40%	3 (2.5)
Cardiac condition	2 (1.7)
SpO$_2$ < 90%	2 (1.7)
Severe RLD	1 (0.8)

ASA: American Society of Anesthesiologists; ppo: predicted postoperative; and RLD: restrictive lung disease.

Table 3 – Distribution of the 120 patients undergoing pulmonary resection by ICU admission status.

Predicted ICU admission, n (%)	Mandatory ICU admission, n (%)		Total
	Yes	No	
Yes	16 (67)	8 (33)	24
No	14 (15)	82 (85)	96
Total	30	90	120

admission vs. elective ICU admission), which affected the results of the validation study.

Therefore, when analyzing studies of prognostic risk models, it is necessary to consider the population they apply to, and when it comes to validation studies, it is necessary to determine whether the circumstances under which they were carried out can be superimposed to those of the original study. However, it is important to bear in mind that most health care facilities do not have the technological means to run sophisticated models, nor do they follow strict inclusion protocols.

What could then be done in this context?

Pieretti et al. [9] used a set of pre-established criteria for predicting the need for ICU admission and obtained satisfactory results. Therefore, at our facility—i.e., a university hospital—we decided to determine whether the use of a set of preoperative clinical variables for predicting the need for ICU admission would be able to accomplish this goal.

The choice of the clinical criteria used for predicting the need for ICU admission was based on data in the literature and on our daily clinical practice. Pneumonectomy accounts for the highest morbidity and mortality rates among the various possible resections. [20-23] ASA physical status 3 means that the patient has severe systemic

Table 4 – Characteristics of the patients for whom ICU admission was not predicted but who required it (mandatory ICU admission).

Patient	Age	ASA physical status	Disease	Resection	Reason for ICU admission
1	66	2	SCC; COPD; arrhythmia; SAH	Left lung	Arrhythmia
2	63	2	SCC	Left lung	Bleeding; HVC; APE; MV
3	58	2	DM; SAH; cystadenoma	LUL	Bleeding; HVC; MV; bronchial fistula
4	70	2	Adenoca; RA; vesical tumor	RUL/seg. VI	Bleeding; hypotension
5	71	2	SCC; neolarynx	RUL	ARF; MV; shock
6	72	2	SCC	LLL/lingula	Bleeding; HVC; MV
7	77	2	Nodule in the RLL	Nodule resection	Hypertensive crisis; arrhythmia
8	54	2	Nodule in the LSD	RUL	Bleeding; hypotension
9	63	2	Metastasis	Metastasectomy	Bleeding; HVC; APE
10	28	2	BE	RUL	Bleeding; hypotension
11	34	2	BE	RUL	Bleeding; HVC; MV
12	62	2	BE	ML/seg. VI	Shock
13	56	2	BE/aspergilloma	RUL	Bronchial fistula; MV; hemothorax; HVC
14	63	2	BE/aspergilloma	LUL	Bleeding; HVC

ASA: American Society of Anesthesiologists; SCC: squamous cell carcinoma; SAH: systemic arterial hypertension; HVC: hypovolemic shock; APE: acute pulmonary edema; MV: mechanical ventilation; DM: diabetes mellitus; LUL: left upper lobe; RA: rheumatoid arthritis; RUL: right upper lobe; seg.: segment; ARF: acute respiratory failure; LLL: left lower lobe; RLL: right lower lobe; BE: bronchiectasis; and ML: middle lobe.

disease resulting in functional limitation in activities of daily living.[14,24-26] Values of < 50% predicted for FEV_1 and FVC, as determined by spirometry, are associated with severe or very severe disease. In a scenario of a patient with reduced functional reserve, who will undergo removal of nonfunctioning parenchyma, the use of ppo-FEV_1 or ppo-DLCO for predicting the need for postoperative ICU admission corrects this distortion, to some extent, and a threshold of 40% has been established by the ACCP guidelines.[12] An SpO_2 on room air at rest < 90% indicates reduced functional reserve and worsening of gas exchange during the removal of still functioning parenchyma.[28,29] Cardiac monitoring as a precautionary measure, the need for which is defined by the cardiologist, is recommended in patients with reduced cardiovascular reserve.[12]

Patients were predicted to require ICU admission because there was a major surgical risk factor or because their clinical status was compromised either by reduced cardiopulmonary reserve or by comorbidities. However, the prediction was incorrect in 8 patients (false positives), and the predictive factors were ppo-DLCO < 40%, severe COPD with an SpO_2 on room air of 88%, and planned pneumonectomy. This finding could signal that, even in large operations, if there are no other risk factors, the patient could be sent to an intermediate care unit and not necessarily to the ICU.

Among the 96 patients for whom the need for ICU admission was not predicted, the non-prediction was incorrect in 14 (false negatives), a situation that is a greater cause for concern than is predicting the need for ICU admission when that is not the case, if the error endangers the postoperative course of such patients. All the complications that justified the patient staying in the ICU occurred during or soon after the surgical procedure, namely: shock and/or hypotension requiring blood transfusion as well as fluid resuscitation; and intraoperative conversion from lobectomy to pneumonectomy. And this scenario could not have been predicted preoperatively.

Although these complications ended up reducing the sensitivity of the criteria used, which was 53.3%, the specificity and negative predictive value of the criteria were encouraging, 91% and 85.4%, respectively, and their accuracy was 81.7%.

These findings make us think that prediction of the need for ICU admission after pulmonary resection should consider the possibility of major bleeding and not only the size of the

operation or the clinical status of the patient. Most studies addressing prediction of the need for ICU admission in pulmonary resection candidates have focused mainly on patients with malignant lung diseases,[7-11] and our study showed that, among patients with bronchiectasis, the rate of intraoperative bleeding was more than twice as high as that among patients with lung cancer.

The major limitation of our study is its sample size, which did not allow the internal validation of the study. The inclusion of patients from a single facility can limit the size of the population sample and preclude the generalization of results. However, it has several advantages: it is convenient for the population that seeks our services; all surgical procedures are performed by the same surgical team; preoperative clinical assessment is also performed by the same team and always in the same way, regardless of whether that is a clinical study or that is simply health care; and the care provided in the ICU and the follow-up care by physiotherapists and by the pain team of the hospital are consistent with our peculiarities and difficulties. Another minimal limitation is the 53.3% sensitivity of the model, a value that reduces its reliability in predicting the need for ICU admission after pulmonary resection. However, this model ensures high specificity and high negative predictive value in predicting which patients will not require ICU admission.

In conclusion, the use of composite measures for predicting the need for ICU admission after pulmonary resection is feasible and accurate, and since this model uses clinical variables that do not require high technology (planned pneumonectomy; severe COPD; severe restrictive lung disease; ppo-FEV_1 or ppo-DLCO < 40%; SpO_2 on room air at rest < 90%; need for cardiac monitoring as a precautionary measure; ASA physical status ≥ 3), it may have wide applicability in daily clinical practice.

References

1. American Thoracic Society. Fair allocation of intensive care unit resources. Am J Respir Crit Care Med. 1997;156(4 Pt 1):1282-301. Erratum in: Am J Respir Crit Care Med 1998;157(2):671.
2. Guidelines for intensive care unit admission, discharge, and triage. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Crit Care Med. 1999; 27(3):633-8. http://dx.doi.org/10.1097/00003246-199903000-00048
3. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009;34(1):17-41. Erratum in: Eur Respir J. 2009;34(3):782. http://dx.doi.org/10.1183/09031936.00184308
4. Thibault GE, Mulley AG, Barnett GO, Goldstein RL, Reder VA, Sherman EL, et al. Medical intensive care: indications, interventions, and outcomes. N Engl J Med. 1980;302(17):938-42. http://dx.doi.org/10.1056/NEJM198004243021703
5. Rosenthal GE, Sirio CA, Shepardson LB, Harper DL, Rotondi AJ, Cooper GS. Use of intensive care units for patients with low severity of illness. Arch Intern Med. 1998;158(10):1144-51. http://dx.doi.org/10.1001/archinte.158.10.1144
6. Ron A, Aronne LJ, Kalb PE, Santini D, Charlson ME. The therapeutic efficacy of critical care units. Identifying subgroups of patients who benefit. Arch Intern Med. 1989;149(2):338-41. http://dx.doi.org/10.1001/archinte.1989.00390020064013
7. Melley DD, Thomson EM, Page SP, Ladas G, Cordingley J, Evans TW. Incidence, duration and causes of intensive care unit admission following pulmonary resection for malignancy. Intensive Care Med. 2006;32(9):1419-22. http://dx.doi.org/10.1007/s00134-006-0269-4
8. Jordan S, Evans TW. Predicting the need for intensive care following lung resection. Thorac Surg Clin. 2008;18(1):61-9. http://dx.doi.org/10.1016/j.thorsurg.2007.11.003
9. Pieretti P, Alifano M, Roche N, Vincenzi M, Forti Parri SN, Zackova M, et al. Predictors of an appropriate admission to an ICU after a major pulmonary resection. Respiration. 2006;73(2):157-65.
10. Brunelli A, Ferguson MK, Rocco G, Pieretti P, Vigneswaran WT, Morgan-Hughes NJ, et al. A scoring system predicting the risk for intensive care unit admission for complications after major lung resection: a multicenter analysis. Ann Thorac Surg. 2008;86(1):213-8. http://dx.doi.org/10.1016/j.athoracsur.2008.03.063
11. Okiror L, Patel N, Kho P, Ladas G, Dusmet M, Jordan S, et al. Predicting risk of intensive care unit admission after resection for non-small cell lung cancer: a validation study. Interact Cardiovasc Thorac Surg. 2012;14(1):31-3. http://dx.doi.org/10.1093/icvts/ivr060
12. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT; American College of Chest Physicians. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):161S-77S.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83. http://dx.doi.org/10.1016/0021-9681(87)90171-8
14. Vacanti CJ, VanHouten RJ, Hill RC. A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. Anesth Analg. 1970;49(4):564-6. http://dx.doi.org/10.1213/00000539-197007000-00010
15. Pereira ED, Fernandes AL, da Silva Anção M, de Araúja Pereres C, Atallah AN, Faresin SM. Prospective assessment of the risk of postoperative pulmonary complications in patients submitted to upper abdominal surgery. Sao Paulo Med J. 1999;117(4):151-60. http://dx.doi.org/10.1590/S1516-31801999000400003
16. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, et al. Prediction of postoperative pulmonary complications

in a population-based surgical cohort. Anesthesiology. 2010;113(6):1338-50. http://dx.doi.org/10.1097/ALN.0b013e3181fc6e0a

17. Gaieski D, Parsons PE, Finlay G. Shock in adults: types, presentation, and diagnostic approach. UptoDate [serial on the Internet] 2014 Aug [cited 2014 Aug 27]. Available from: http://www.uptodate.com/contents/shock-in-adults-types-presentation-and-diagnostic-approach

18. Sociedade Brasileira de Pneumologia e Tisiologia. Oxigenoterapia domiciliar prolongada (ODP). J Pneumol. 2000; 26(6):341-50. http://dx.doi.org/10.1590/S0102-35862000000600011

19. Hiramatsu M, Shiraishi Y, Nakajima Y, Miyaoka E, Katsuragi N, Kita H, et al. Risk factors that affect the surgical outcome in the management of focal bronchiectasis in a developed country. Ann Thorac Surg. 2012;93(1):245-50. http://dx.doi.org/10.1016/j.athoracsur.2011.08.077

20. Miller DL, Deschamps C, Jenkins GD, Bernard A, Allen MS, Pairolero PC. Completion pneumonectomy: factors affecting operative mortality and cardiopulmonary morbidity. Ann Thorac Surg. 2002;74(3):876-83; discussion 883-4. http://dx.doi.org/10.1016/S0003-4975(02)03855-9

21. Sherwood JT, Mitchell JD, Pomerantz M. Completion pneumonectomy for chronic mycobacterial disease. J Thorac Cardiovasc Surg. 2005;129(6):1258-65. http://dx.doi.org/10.1016/j.jtcvs.2004.12.053

22. Bernard A, Deschamps C, Allen MS, Miller DL, Trastek VF, Jenkins GD, et al. Pneumonectomy for malignant disease: factors affecting early morbidity and mortality. J Thorac Cardiovasc Surg. 2001;121(6):1076-82. http://dx.doi.org/10.1067/mtc.2001.114350

23. Algar FJ, Alvarez A, Salvatierra A, Baamonde C, Aranda JL, López-Pujol FJ. Predicting pulmonary complications after pneumonectomy for lung cancer. Eur J Cardiothorac Surg. 2003;23(2):201-8. http://dx.doi.org/10.1016/S1010-7940(02)00719-4

24. Saklad M. Grading of patients for surgical procedures. Anesthesiology. 1941;2:281-4. http://dx.doi.org/10.1097/00000542-194105000-00004

25. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. Anesthesiology. 1978;49(4):239-43. http://dx.doi.org/10.1097/00000542-197810000-00003

26. Aronson WL, McAuliffe MS, Miller K. Variability in the American Society of Anesthesiologists Physical Status Classification Scale. AANA J. 2003;71(4):265-74.

27. Brunelli A, Refai M, Xiumé F, Salati M, Marasco R, Sciarra V, et al. Oxygen desaturation during maximal stair-climbing test and postoperative complications after major lung resections. Eur J Cardiothorac Surg. 2008;33(1):77-82. http://dx.doi.org/10.1016/j.ejcts.2007.09.028

28. Markos J, Mullan BP, Hillman DR, Musk AW, Antico VF, Lovegrove FT, et al. Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis. 1989;139(4):902-10. http://dx.doi.org/10.1164/ajrccm/139.4.902

29. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e166S-90S. Erratum in: Chest. 2014;145(2):437.

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Chronic intermittent hypoxia increases encoding pigment epithelium-derived factor gene expression, although not that of the protein itself, in the temporal cortex of rats*,**

Hipóxia intermitente crônica aumenta a expressão gênica, mas não proteica, de *pigment epithelium-derived factor*, no córtex temporal de ratos

Guilherme Silva Julian, Renato Watanabe de Oliveira, Vanessa Manchim Favaro, Maria Gabriela Menezes de Oliveira, Juliana Cini Perry, Sergio Tufik, Jair Ribeiro Chagas

Abstract

Objective: Obstructive sleep apnea syndrome is mainly characterized by intermittent hypoxia (IH) during sleep, being associated with several complications. Exposure to IH is the most widely used animal model of sleep apnea, short-term IH exposure resulting in cognitive and neuronal impairment. Pigment epithelium-derived factor (PEDF) is a hypoxia-sensitive factor acting as a neurotrophic, neuroprotective, and antiangiogenic agent. Our study analyzed performance on learning and cognitive tasks, as well as *PEDF* gene expression and PEDF protein expression in specific brain structures, in rats exposed to long-term IH. **Methods:** Male Wistar rats were exposed to IH (oxygen concentrations of 21-5%) for 6 weeks—the chronic IH (CIH) group—or normoxia for 6 weeks—the control group. After CIH exposure, a group of rats were allowed to recover under normoxic conditions for 2 weeks (the CIH+N group). All rats underwent the Morris water maze test for learning and memory, *PEDF* gene expression and PEDF protein expression in the hippocampus, frontal cortex, and temporal cortex being subsequently assessed. **Results:** The CIH and CIH+N groups showed increased *PEDF* gene expression in the temporal cortex, PEDF protein expression remaining unaltered. *PEDF* gene expression and PEDF protein expression remained unaltered in the frontal cortex and hippocampus. Long-term exposure to IH did not affect cognitive function. **Conclusions:** Long-term exposure to IH selectively increases *PEDF* gene expression at the transcriptional level, although only in the temporal cortex. This increase is probably a protective mechanism against IH-induced injury.

Keywords: Sleep apnea, central; Disease models, animal; Cognition; Sleep; Sleep apnea, obstructive.

Resumo

Objetivo: A síndrome da apneia obstrutiva do sono caracteriza-se principalmente por episódios de hipóxia intermitente (HI) durante o sono e associa-se a diversas complicações. A exposição à HI é o mais usado modelo animal de apneia do sono, e protocolos de curta duração causam diversos prejuízos cognitivos e neuronais. *Pigment epithelium-derived factor* (PEDF, fator derivado do epitélio pigmentado) é um fator neurotrófico, neuroprotetor e antiangiogênico sensível à hipóxia celular. Nosso estudo analisou o desempenho em tarefas cognitivas e de aprendizagem, bem como a expressão do gene *PEDF* e da proteína PEDF em estruturas cerebrais específicas em ratos expostos a HI de longa duração. **Métodos:** Ratos Wistar foram expostos a HI (21-5% de oxigênio) durante 6 semanas — o grupo HI crônica (HIC) — ou a normóxia durante 6 semanas — o grupo controle. Após a exposição à HIC, um grupo de ratos foi exposto a normóxia durante 2 semanas (o grupo HIC+N). Todos os animais foram submetidos ao labirinto aquático de Morris para avaliação de memória e aprendizado; avaliou-se também a expressão do gene *PEDF* e da proteína PEDF no hipocampo e nos córtices frontal e temporal. **Resultados:** Os grupos HIC e HIC+N apresentaram um aumento de expressão do gene *PEDF* no córtex temporal, porém sem aumento dos níveis proteicos. A expressão do gene *PEDF* e da proteína PEDF manteve-se inalterada nas demais estruturas. A exposição de longa duração à HI não afetou a função cognitiva. **Conclusões:** A exposição de longa duração à HI aumenta seletivamente a expressão do gene *PEDF* ao nível transcricional, embora apenas no córtex temporal. Esse aumento é provavelmente um mecanismo de proteção contra a HI.

Descritores: Apneia do sono tipo central; Modelos animais de doenças; Sono; Cognição; Apneia do sono tipo obstrutiva.

Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and is a public health issue because of its high prevalence.[1,2] It is characterized by recurrent episodes of partial or complete upper airway obstruction, leading to sleep fragmentation, hypercapnia, and nocturnal intermittent hypoxia (IH). A number of animal models of OSA have been developed over the years,[3] most of which have focused on IH. The IH model produces several effects that are similar to those of OSA, including cognitive impairment, changes in sleep architecture, insulin resistance, and hypertension.[4-10] This suggests that IH plays an important role in OSA,[11] affecting even cognition.

Learning and cognition require a process known as synaptic plasticity, which is the ability of synapses to strengthen or weaken their connections.[12] Several factors control synaptic plasticity, including neurotransmitters and neurotrophic factors that play an essential role in the growth and survival of developing neurons. One such factor is pigment epithelium-derived factor (PEDF), which has antiangiogenic, neuroprotective, and neurotrophic activity.

As a neuroprotective agent, PEDF reduces glutamate-mediated excitotoxicity[13-15] and attenuates ischemic brain damage.[16] As a neurotrophic agent, PEDF induces the expression of other factors, such as brain-derived neurotrophic factor, glial cell line–derived neurotrophic factor, and nerve growth factor,[17] and increases the formation of dendritic spines.[18] The sensitivity of PEDF to hypoxic exposure has been shown to vary,[19,20] with divergent results regarding the relationship between PEDF and oxygen levels.

Although the effects of short-term IH on learning, cognition, memory, and neurotrophic factors are known,[21] the effects of long-term IH remain unclear. Therefore, in order to determine the relationships among PEDF, chronic intermittent hypoxia (CIH), and memory, as well as to improve the understanding of the role of PEDF in CIH, the present study examined spatial memory, *PEDF* gene expression, and PEDF protein expression in a rat model of CIH. Indeed, the effects of in vivo hypoxia models on PEDF messenger RNA (mRNA) and protein levels remain unknown.

Methods

In the present study, we used 45 adult male Wistar Hannover rats provided by the Federal University of São Paulo *Centro de Desenvolvimento de Modelos Experimentais para Medicina e Biologia* (CEDEME, Center for the Development of Biological and Biomedical Models), located in the city of São Paulo, Brazil. The study was approved by the Animal Research Ethics Committee of the Federal University of São Paulo, located in the city of São Paulo, Brazil (Protocol no 2025/11).

All animals were housed at 22°C on a 12/12-h light/dark cycle (lights on at 7:00 a.m. and off at 7:00 p.m.) and were given *ad libitum* access to food and water. The rats were randomly assigned to the control group (n = 15); the CIH group (n = 15), which comprised animals exposed to IH for 6 weeks[22]; or the CIH+N group, which comprised animals exposed to 6 weeks of IH followed by 2 weeks of recovery in normoxia.[22]

The Morris water maze (MWM) test was performed in a separate room in a black circular pool (of 200 cm in diameter by 40 cm in height) filled with water at approximately 23°C to a depth of 25 cm. For animal orientation, distinct visual cues were placed on each wall of the room. A black platform of 10 cm in diameter was placed 2 cm below the surface and fixed in the center of the target quadrant.

Two separate tests were performed. The first involved 8 control rats and the 15 rats in the CIH group, and the second involved 7 control rats and the 15 rats in the CIH+N group. Spatial learning sessions were conducted on five consecutive days, in the last week of exposure to CIH or CIH+N. During the test week, the rats in the CIH group were exposed to IH for 8 h/day. The spatial learning sessions consisted of four 1-min trials for each animal, with a 1-min interval between trials. Rats began the MWM from different quadrants in the pool at the start of each trial.

After the last training day, all rats underwent a 1-min trial of free swimming in the MWM without the platform. The ratio between the time spent in the target quadrant and the time spent in other quadrants was used in order to determine spatial memory. The tests were performed one day after the last CIH exposure for the CIH group and after the 2 weeks of normoxia for the CIH+N group. Each group had its own control group. All trials were analyzed by identifying contrast between

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the (white) animal and the (black) tank, with the Noldus EthoVision XT video tracking software, version 7.0 (Noldus Information Technology Inc., Leesburg, VA, USA).

Immediately after the MWM test, all rats were euthanized by rapid decapitation. The brains were rapidly removed and dissected to remove the hippocampus, frontal cortex, and temporal cortex. All tissues were rapidly dissected on dry ice and stored at −80°C until RNA extraction. It has been reported that CIH affects spatial memory and learning,[6,9,23] which is why we studied PEDF expression in the hippocampus, frontal cortex, and temporal cortex (areas related to spatial and visual learning).

For all structures, total RNA extraction was performed with TRIzol® (Thermo Fisher Scientific Inc., Waltham, MA, USA), in accordance with the manufacturer instructions. After extraction, RNA was treated with DNAse 1 (Thermo Fisher Scientific Inc.), its quality and integrity being evaluated by visualization of rRNA after agarose gel electrophoresis. Quantitation was performed by means of spectrophotometry at 260 nm (NanoDrop, Wilmington, DE, USA), and purity was estimated by a 260/280-nm ratio > 1.8. One µg of RNA from each dissected structure was reverse transcribed with the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA), in accordance with the manufacturer instructions.

Each cDNA was used as a template for real-time PCR amplification with fluorescent-labeled probes (TaqMan®; Applied Biosystems) and the 7500 Real-Time PCR System (Applied Biosystems) for detection. The level of expression of the *PEDF* gene (Rn00709999_m1) was determined by using *beta-actin* (Rn00667869_m1) and *glyceraldehyde-3-phosphate dehydrogenase* (Rn01775763_g1) as housekeeping genes.[22] Each reaction was performed in a final volume of 20 µL, i.e., 1 µL of cDNA diluted in water and 19 µL of master mix (1 µL of TaqMan® assay probe, 10 µL of TaqMan® Universal PCR Master Mix, and 8 µL of water), threshold cycle values being maintained between 15.0 and 33.0. All samples were run in triplicate, and average values were calculated.

For Western blotting analyses, all tissues were homogenized in lysis buffer (50 mM Tris-HCl, pH 7.4; 100 mM NaCl; 0.1% Triton X-100 [The Dow Chemical Company, Midland, MI, USA]; 1 mM EDTA; and a protease inhibitor cocktail

[Sigma-Aldrich, St. Louis, MO, USA]), 10 µL of lysis buffer being used for each 1 mg of tissue. After homogenization, the lysate was cleared by centrifugation at 13,000 rpm for 10 min at 4°C, the supernatant was collected, and supernatant proteins were quantified by the Lowry method (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

One hundred micrograms of protein extract from all brain structures were incubated at 95°C for 10 min with sample buffer, subjected to SDS-PAGE (10%), and transferred to a 0.2-µm nitrocellulose membrane (Hybond ECL; GE Healthcare, Chalfont St Giles, UK). After protein transfer, the membrane was blocked in a solution of 5% skim milk in TBS with Tween 20 for 2 h at room temperature and incubated overnight at 4°C with PEDF primary antibody (BioProducts MD, LLC, Middletown, MD, USA) and glyceraldehyde-3-phosphate dehydrogenase primary antibody (Sigma-Aldrich) at 1:500 and 1:1,000,000 dilutions, respectively. The membrane was developed with goat anti-rabbit secondary antibody, labeled with Alexa Fluor® 680 fluorescent dye (Thermo Fisher Scientific Inc.), incubated for 1 h in blocking buffer at 1:10,000 dilution, washed with TBS with Tween 20, and scanned on an Odyssey Infrared Imaging System (LI-COR Biosciences, Lincoln, NE, USA). The images were analyzed with the Odyssey Application Software, version 1.2 (LI-COR Biosciences).

All data were initially analyzed for normality of distribution and homogeneity of variance with the Kolmogorov-Smirnov test and Levene's test, respectively. When data were not normally distributed or heterogeneity of variance was identified, a Z score correction was performed, and the groups were compared by one-way ANOVA followed by Dunnett's post hoc test, when necessary. With regard to the Western blotting results, the groups were compared by the Kruskal-Wallis test because of the small number of animals per group. With regard to the MWM test results, the groups were compared by repeated measures ANOVA, followed by Tukey's post hoc test. All data were expressed as mean ± standard error of the mean. The level of significance was set at $p \leq 0.05$.

Results

All rats learned the MWM, the difference between their performance during the training phase and their performance during the acquisition

phase being significantly different. A continuous decrease in latency time shows the learning process ($F_{1,17}$ = 32.561, p < 0.001 for the control group vs. the CIH group during the training phase; $F_{1,23}$ = 38.916, p < 0.001 for the control group vs. the CIH+N group during the training phase). As can be seen in Figures 1 and 2, neither CIH nor CIH+N had any effect on the learning process ($F_{1,17}$ = 1.393, p = 0.246 for the CIH group during the acquisition phase vs. the CIH group during the training phase; $F_{1,23}$ = 1.837, p = 0.128 for the CIH+N group during the acquisition phase vs. the CIH+N group during the training phase), with no evidence of learning impairment in either group when compared with the control group.

Memory retention can be evaluated by removing the platform (probe trials). A probe trial shows whether animals learned the task and whether
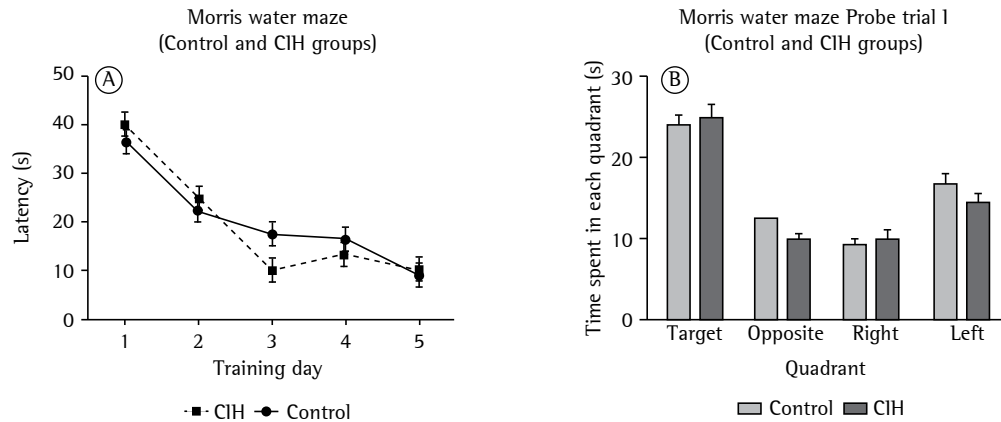
Figure 1 – Effects of chronic intermittent hypoxia (CIH) on spatial learning and memory. In A, comparison between Wistar rats exposed to CIH (the CIH group) and control rats (the control group) in terms of their performance during Morris water maze (MWM) testing. For 5 consecutive days, rats underwent four 1-min trials, with a 1-min interval between trials. No statistically significant differences were observed. All data are presented as mean ± SD. Two-way repeated measures ANOVA followed by Tukey's post hoc test. In B, comparison between the control and CIH groups in terms of the time spent in each MWM quadrant, in order to evaluate spatial memory on day 6. No statistically significant differences were observed. All data are expressed as mean ± standard error of the mean.
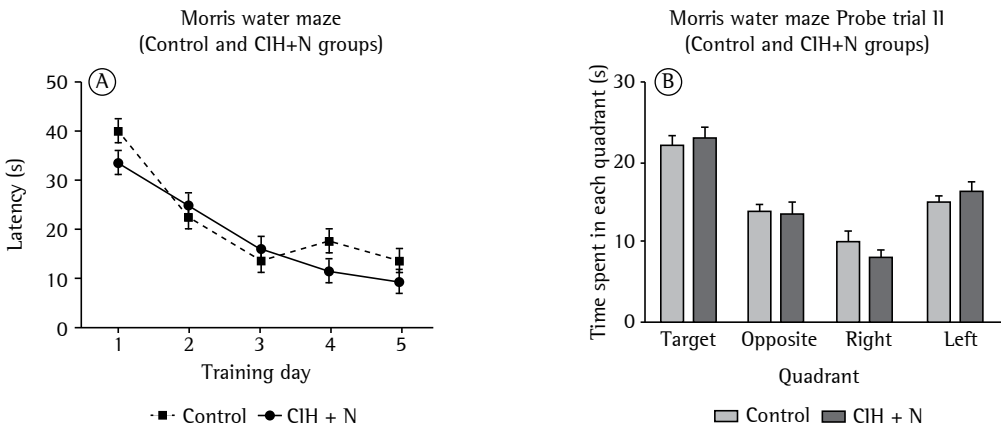
Figure 2 – Effects of exposure to chronic intermittent hypoxia (CIH) followed by 2 weeks of normoxia on spatial learning and memory. In A,, comparison between Wistar rats exposed to CIH plus two weeks of normoxia (the CIH+N group) and control rats (the control group) in terms of their performance during Morris water maze (MWM) testing. For 5 consecutive days, rats underwent four 1-min trials, with a 1-min interval between trials. No statistically significant differences were observed. All data are presented as mean ± SD. Two-way repeated measures ANOVA followed by Tukey's post hoc test. In B, comparison between the control and CIH+N groups in terms of the time spent in each MWM quadrant, in order to evaluate spatial memory on day 6. No statistically significant differences were observed. All data are expressed as mean ± standard error of the mean.

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Table 1 – Comparison of different chronic intermittent hypoxia protocols in terms of cognitive effects, evaluation method, minimum oxygen concentration, cycle duration, and exposure duration.

Author	Year of publication	Cognitive effects	Evaluation method	Minimum oxygen concentration	Cycle duration	Exposure duration
Gozal et al.[9]	2001	Impaired learning and spatial memory	MWM task	10%	1.5 min	14 days
Row et al.[25]	2002	Impaired learning and spatial memory	MWM task	10%	1.5 min	14 days
Goldbart et al.[6]	2003	Impaired learning and spatial memory; impaired CREB phosphorylation	MWM task and CREB phosphorylation	10%	1.5 min	1-30 days
Row et al.[23]	2007	Impaired working memory	Modified MWM task	10%	1.5 min	1-14 days
Perry et al.[28]	2008	Unaltered amygdala-dependent memory	Inhibitory avoidance task	10%	2 min	3-21 days
Wall et al.[26]	2013	Reduced LTP	In vitro measurement of LTP	5%	1.5 min	8 days
Shiota et al.[27]	2013	Unaltered learning and spatial-memory	MWM task	5%	10 min	8 weeks
Julian et al.[22]	-	Unaltered learning and spatial memory	MWM task	5%	3 min	6 weeks and 6 weeks + 2 weeks recovery

MWM: Morris water maze; LTP: long-term potentiation; and CREB: cAMP response element binding protein.

they were able to retain learned information. On probe trials I and II, no significant differences were observed between the CIH and control groups or between the CIH+N and control groups in terms of the time spent in the target quadrant ($F_{1,20} = 0.122$; p = 0.731 and $F_{1,23} = 0.278$; p = 0.603, respectively; Figures 1 and 2), showing that neither CIH nor CIH+N affected learning and memory retention processes.

Exposure to CIH did not affect *PEDF* gene expression in the hippocampus and frontal cortex ($F_{2,21} = 1.408$; p = 0.267 and $F_{2,21} = 2.689$; p = 0.091, respectively), mRNA levels having remained unaltered after 6 weeks of IH. In addition, *PEDF* gene expression remained unaltered after 6 weeks of IH followed by 2 weeks of recovery in normoxia, showing that although hypoxia induces angiogenesis, CIH and CIH+N did not affect the expression of *PEDF*, which is an important neurotrophic and antiangiogenic factor.

The relative mRNA expression of *PEDF* in the temporal cortex increased 1.5-fold after 6 weeks of exposure to IH ($F_{2,20} = 6.583$; p = 0.006; Dunnett's post hoc test: p = 0,004). After 2 weeks of recovery in normoxia, *PEDF* mRNA did not return to normal, being 1.3-fold higher in the CIH+N group than in the control group (Dunnet's post hoc test; p = 0.029; Figure 3). This suggests that it takes a long time for the

effects of CIH to subside, or even that they are irreversible.

There were no significant changes in PEDF protein levels in the hippocampus (H(2) = 1.192; p = 0.551), frontal cortex (H(2) = 0.38; p = 0.981), or temporal cortex (H(2) = 2.577; p = 0.276) of animals exposed to CIH or CIH+N. Although *PEDF* gene expression in the temporal cortex increased 1.5-fold, the protein levels remained unaltered (Figure 4). This might be due to the fact that Western blotting is less sensitive than real-time PCR, which is a much more accurate method.

Discussion

Short-term IH models have several neurological implications: increased hippocampal and cortical apoptosis[9]; inhibition of cAMP response element binding protein phosphorylation; and learning and memory impairment.[6] Our results show that exposure to CIH and CIH+N did not affect learning and retention in a spatial memory task, being inconsistent with those of studies involving short-term exposure to IH.[6,9,23-26] This might be due to differences in the hypoxia protocol (including differences in cycle and exposure duration) and in oxygen concentration. Studies involving short-term (≤ 30-day) exposure to IH
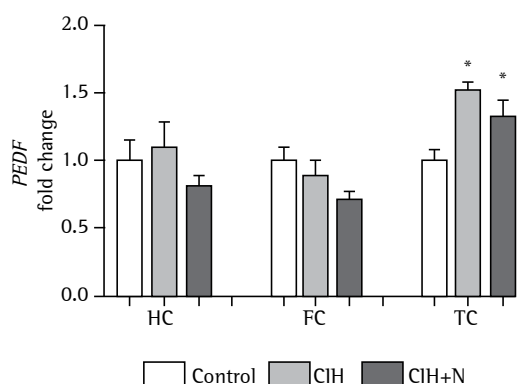
Figure 3 – Relative *pigment epithelium-derived factor* (*PEDF*) gene expression in the central nervous system, *glyceraldehyde-3-phosphate dehydrogenase* and *beta-actin* being used as housekeeping genes. *PEDF* gene expression was found to be increased, although only in the temporal cortex, in the chronic intermittent hypoxia (CIH) and CIH plus 2 weeks of normoxia (CIH+N) groups when compared with the control group. *p < 0.05 in comparison with the control group; one-way ANOVA followed by Dunnett's post hoc test. All data are expressed as mean ± standard error of the mean. HC: hippocampus; FC: frontal cortex; and TC: temporal cortex.
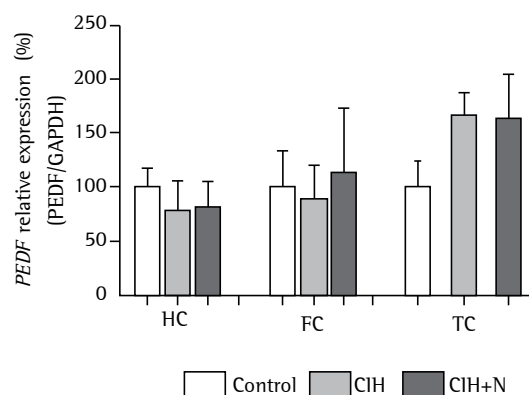
Figure 4 – Relative pigment epithelium-derived factor (PEDF) protein expression in the central nervous system, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) being used as loading control. There were no significant differences in PEDF levels among the brain structures studied (p < 0.05). There were no significant differences in PEDF levels among the control, chronic intermittent hypoxia (CIH), and CIH plus 2 weeks of normoxia (CIH+N) groups (p < 0.05). One-way ANOVA. All data are expressed as mean ± standard error of the mean. HC: hippocampus; FC: frontal cortex; and TC: temporal cortex.

and oxygen concentrations ranging from 21% to 10% have shown evidence of memory impairment (Table 1). A comparison of the findings of the studies described in Table 1 shows that cognitive response varies according to the IH protocol.

Studies have shown that memory retention processes are not affected by CIH. Shiota et al.[27] demonstrated that exposure to IH for 8 weeks with varying oxygen concentrations (ranging from 21% to 5%) did not affect learning and retention in the MWM task. Golbart et al.[6] evaluated spatial reference memory in rats and demonstrated that short-term exposure to IH selectively affects memory and cAMP response element binding protein phosphorylation, whereas long-term IH exposure does not. Perry et al.[28] reported that rats exposed to IH for 3 weeks did not show impaired acquisition/retention in an inhibitory avoidance task, an amygdala-dependent memory task, or an activity chamber.

The fact that long-term exposure to IH does not result in memory impairment might be due to neural adaptation after short-term exposure to IH; although short-term exposure to IH affects learning and memory, long-term exposure does not. Therefore, IH models might not be the best animal models to study the cognitive effects of OSA, because of a possible adaptation response in animals.[29]

Our study showed that neither CIH nor CIH+N affected *PEDF* gene expression or PEDF protein expression in the hippocampus. These results corroborate our behavioral results, which suggest that the hippocampus was able to exert its spatial learning function normally. Because PEDF has important neurotrophic and neuroprotective functions, PEDF levels are expected to remain unaltered in cases of unaltered learning and memory.

Our study showed that *PEDF* gene expression in the temporal cortex increased 1.5-fold in the CIH group and 1.3-fold in the CIH+N group. This increase in *PEDF* gene expression is similar to that observed in exposure to severe sustained hypoxia (an oxygen concentration of 0.2%) in vitro; increased *PEDF* gene expression can be a cellular defense mechanism to ensure cell survival under severe hypoxic conditions.[30] In addition, a period of 2 weeks of recovery in normoxia after exposure to CIH is not enough to normalize *PEDF* gene expression, showing that CIH-induced changes can be long-lasting. [31] Although *PEDF* gene expression increased in the CIH and CIH+N groups, PEDF protein levels did not change. Divergent gene and protein

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expression profiles following severe sustained hypoxia have been reported, protein levels having remained unaltered and genetic expression having increased 2.0-fold.[30]

The effects of CIH on *PEDF* gene expression were not reversed after 2 weeks of recovery in normoxia in the CIH+N group. This underscores the fact that CIH has persistent effects on biochemical and oxidative parameters in the brainstem and forebrain, which are related to hypersomnolence.[31]

The unaltered protein levels in the present study might also be due to increased PEDF catabolism, given that matrix metalloproteinases 2 and 9 show increased activity in hypoxic conditions and are involved in PEDF degradation. Therefore, increased PEDF levels followed by increased activity of matrix metalloproteinases 2 and 9 might result in unaltered PEDF protein levels.[32] Conversely, VEGF, which is a potent angiogenic factor, is expressed differently among brain regions, VEGF levels remaining unaltered in the temporal cortex and being increased in the frontal cortex after exposure to IH. In addition, VEGF regulates PEDF expression, supporting the idea of a negative feedback loop in the protein.[33]

The present study has some limitations. One is that CIH models simulate only one of the four major characteristics of OSA. Another limitation is that our CIH protocol included a low number of IH events per hour (simulating mild OSA). In summary, long-term exposure to IH selectively increased *PEDF* gene expression at the transcriptional level, although only in the temporal cortex. In the hippocampus and frontal cortex, *PEDF* gene expression remained unaltered. Protein expression remained unaltered in all structures. Exposure to CIH did not affect learning and memory on the MWM task. This selective increase in gene expression in the temporal cortex might be a protective mechanism against the neuronal injury caused by CIH. The results of the present study suggest that the effects that long-term exposure to IH has on memory are reversible.

References

1. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441-6. http://dx.doi.org/10.1016/j.sleep.2009.10.005
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006-14. http://dx.doi.org/10.1093/aje/kws342
3. Dematteis M, Godin-Ribuot D, Arnaud C, Ribuot C, Stanke-Labesque F, Pépin JL, et al. Cardiovascular consequences of sleep-disordered breathing: contribution of animal models to understanding the human disease. ILAR J. 2009;50(3):262-81. http://dx.doi.org/10.1093/ilar.50.3.262
4. Dumitrascu R, Heitmann J, Seeger W, Weissmann N, Schulz R. Obstructive sleep apnea, oxidative stress and cardiovascular disease: lessons from animal studies. Oxid Med Cell Longev. 2013;2013:234631. http://dx.doi.org/10.1155/2013/234631
5. Iyer SR. Sleep and type 2 diabetes mellitus- clinical implications. J Assoc Physicians India. 2012;60:42-7.
6. Goldbart A, Row B, Kheirandish L, Schurr A, Gozal E, Guo S., et al. Intermittent hypoxic exposure during light phase induces changes in cAMP response element binding protein activity in the rat CA1 hippocampal region: water maze performance correlates. Neuroscience. 2003;122(3):585-90. http://dx.doi.org/10.1016/j.neuroscience.2003.08.054
7. Carreras A, Kayali F, Zhang J, Hirotsu C, Wang Y, Gozal D. Metabolic effects of intermittent hypoxia in mice: steady versus high-frequency applied hypoxia daily during the rest period. Am J Physiol Regul Integr Comp Physiol. 20121;303(7):R700-9.
8. Perry JC, Bergamaschi CT, Campos RR, Andersen ML, Casarini DE, Tufik S. Differential sympathetic activation induced by intermittent hypoxia and sleep loss in rats: Action of angiotensin (1-7). Auton Neurosci. 2011;160(1-2):32-6 http://dx.doi.org/10.1016/j.autneu.2010.11.006
9. Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. J Neurosci. 2001;21(7):2442-50.
10. Polotsky VY, Rubin AE, Balbir A, Dean T, Smith PL, Schwartz AR, et al. Intermittent hypoxia causes REM sleep deficits and decreases EEG delta power in NREM sleep in the C57BL/6J mouse. Sleep Med. 2006;7(1):7-16. http://dx.doi.org/10.1016/j.sleep.2005.06.006
11. Sunderram J, Androulakis IP. Molecular mechanisms of chronic intermittent hypoxia and hypertension. Crit Rev Biomed Eng. 2012;40(4):265-78. http://dx.doi.org/10.1615/CritRevBiomedEng.v40.i4.30
12. Poon VY, Choi S, Park M. Growth factors in synaptic function. Front Synaptic Neurosci. 2013;5:6. http://dx.doi.org/10.3389/fnsyn.2013.00006
13. Sanagi T, Yabe T, Yamada H. Adenoviral gene delivery of pigment epithelium-derived factor protects striatal neurons from quinolinic acid-induced excitotoxicity. J Neuropathol Exp Neurol. 2010;69(3):224-33. http://dx.doi.org/10.1097/NEN.0b013e3181cfc46f
14. Taniwaki T, Hirashima N, Becerra SP, Chader GJ, Etcheberrigaray R, Schwartz JP. Pigment epithelium-derived factor protects cultured cerebellar granule cells against glutamate-induced neurotoxicity. J Neurochem. 1997;68(1):26-32. http://dx.doi.org/10.1046/j.1471-4159.1997.68010026.x
15. Yabe T, Sanagi T, Yamada H. The neuroprotective role of PEDF: implication for the therapy of neurological disorders. Curr Mol Med. 2010;10(3):259-66. http://dx.doi.org/10.2174/156652410791065354
16. Sanagi T, Yabe T, Yamada H. Gene transfer of PEDF attenuates ischemic brain damage in the rat middle cerebral

artery occlusion model. J Neurochem. 2008;106(4):1841-54. http://dx.doi.org/10.1111/j.1471-4159.2008.05529.x

17. Yabe T, Wilson D, Schwartz JP. NFkappaB activation is required for the neuroprotective effects of pigment epithelium-derived factor (PEDF) on cerebellar granule neurons. J Biol Chem. 2001;276(46):43313-9. http://dx.doi.org/10.1074/jbc.M107831200

18. Smith ND, Schulze-Hoepfner FT, Veliceasa D, Filleur S, Shareef S, Huang L, et al. Pigment epithelium-derived factor and interleukin-6 control prostate neuroendocrine differentiation via feed-forward mechanism. J Urol. 2008;179(6):2427-34. http://dx.doi.org/10.1016/j.juro.2008.01.081

19. Yang XM, Yafai Y, Wiedemann P, Kuhrt H, Wang Y-S, Reichenbach A, et al. Hypoxia-induced upregulation of pigment epithelium-derived factor by retinal glial (Müller) cells. J Neurosci Res. 2012;90(1):257-66. http://dx.doi.org/10.1002/jnr.22732

20. Fernández-Barral A, Orgaz JL, Gomez V, del Peso L, Calzada MJ, Jiménez B. Hypoxia negatively regulates antimetastatic PEDF in melanoma cells by a hypoxia inducible factor-independent, autophagy dependent mechanism. PLoS One. 2012;7(3):e32989. http://dx.doi.org/10.1371/journal.pone.0032989

21. Xie H, Yung W. Chronic intermittent hypoxia-induced deficits in synaptic plasticity and neurocognitive functions: a role for brain-derived neurotrophic factor. Acta Pharmacol Sin. 2012;33(1):5-10. http://dx.doi.org/10.1038/aps.2011.184

22. Julian GS, de Oliveira RW, Perry JC, Tufik S, Chagas JR. Validation of housekeeping genes in the brains of rats submitted to chronic intermittent hypoxia, a sleep apnea model. PLoS One. 2014;9(10):e109902. http://dx.doi.org/10.1371/journal.pone.0109902

23. Row BW, Kheirandish L, Cheng Y, Rowell PP, Gozal D. Impaired spatial working memory and altered choline acetyltransferase (CHAT) immunoreactivity and nicotinic receptor binding in rats exposed to intermittent hypoxia during sleep. Behav Brain Res. 2007;177(2):308-14. http://dx.doi.org/10.1016/j.bbr.2006.11.028

24. Shan X, Chi L, Ke Y, Luo C, Qian S, Gozal D, et al. Manganese superoxide dismutase protects mouse cortical neurons from chronic intermittent hypoxia-mediated oxidative damage. Neurobiol Dis. 2007;28(2):206-15 http://dx.doi.org/10.1016/j.nbd.2007.07.013

25. Row BW, Kheirandish L, Neville JJ, Gozal D. Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. Pediatr Res. 2002;52(3):449-53. http://dx.doi.org/10.1203/00006450-200209000-00024

26. Wall AM, Corcoran AE, O'Halloran KD, O'Connor JJ. Effects of prolyl-hydroxylase inhibition and chronic intermittent hypoxia on synaptic transmission and plasticity in the rat CA1 and dentate gyrus. Neurobiol Dis. 2014;62:8-17. http://dx.doi.org/10.1016/j.nbd.2013.08.016

27. Shiota S, Takekawa H, Matsumoto SE, Takeda K, Nurwidya F, Yoshioka Y, et al. Chronic intermittent hypoxia/reoxygenation facilitate amyloid-β generation in mice. J Alzheimers Dis. 2013;37(2):325-33.

28. Perry JC, D'Almeida V, Lima MM, Godoi FR, Vital MA, Oliveira MG, et al. Intermittent hypoxia and sleep restriction: motor, cognitive and neurochemical alterations in rats. Behav Brain Res. 2008;189(2):373-80. http://dx.doi.org/10.1016/j.bbr.2008.01.014

29. Lavie L, Lavie P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. Med Hypotheses. 2006;66(6):1069-73. http://dx.doi.org/10.1016/j.mehy.2005.10.033

30. Lange J, Yafai Y, Reichenbach A, Wiedemann P, Eichler W. Regulation of pigment epithelium-derived factor production and release by retinal glial (Müller) cells under hypoxia. Invest Ophthalmol Vis Sci. 2008;49(11):5161-7. http://dx.doi.org/10.1167/iovs.08-2201

31. Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, et al. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. Sleep. 2004;27(2):194-201.

32. Notari L, Miller A, Martínez A, Amaral J, Ju M, Robinson G, et al. Pigment epithelium-derived factor is a substrate for matrix metalloproteinase type 2 and type 9: implications for downregulation in hypoxia. Invest Ophthalmol Vis Sci. 2005;46(8):2736-47. http://dx.doi.org/10.1167/iovs.04-1489

33. Kalaria RN, Spoors L, Laude EA, Emery CJ, Thwaites-Bee D, Fairlie J, et al. Hypoxia of sleep apnoea : cardiopulmonary and cerebral changes after intermittent hypoxia in rats. Respir Physiol Neurobiol. 2004;140(1):53-62. http://dx.doi.org/10.1016/j.resp.2004.01.003

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Community-acquired pneumonia: economics of inpatient medical care vis-à-vis clinical severity*,**

Pneumonia adquirida na comunidade: economia de cuidados médicos em regime de internamento, em relação à gravidade clínica

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Abstract

Objective: To assess the direct and indirect costs of diagnosing and treating community-acquired pneumonia (CAP), correlating those costs with CAP severity at diagnosis and identifying the major cost drivers. **Methods:** This was a prospective cost analysis study using bottom-up costing. Clinical severity and mortality risk were assessed with the pneumonia severity index (PSI) and the mental Confusion-Urea-Respiratory rate-Blood pressure-age ≥ 65 years (CURB-65) scale, respectively. The sample comprised 95 inpatients hospitalized for newly diagnosed CAP. The analysis was run from a societal perspective with a time horizon of one year. **Results:** Expressed as mean ± standard deviation, in Euros, the direct and indirect medical costs per CAP patient were 696 ± 531 and 410 ± 283, respectively, the total per-patient cost therefore being 1,106 ± 657. The combined budget impact of our patient cohort, in Euros, was 105,087 (66,109 and 38,979 in direct and indirect costs, respectively). The major cost drivers, in descending order, were the opportunity cost (lost productivity); diagnosis and treatment of comorbidities; and administration of medications, oxygen, and blood derivatives. The CURB-65 and PSI scores both correlated with the indirect costs of CAP treatment. The PSI score correlated positively with the overall frequency of use of health care services. Neither score showed any clear relationship with the direct costs of CAP treatment. **Conclusions:** Clinical severity at admission appears to be unrelated to the costs of CAP treatment. This is mostly attributable to unwarranted hospital admission (or unnecessarily long hospital stays) in cases of mild pneumonia, as well as to over-prescription of antibiotics. Authorities should strive to improve adherence to guidelines and promote cost-effective prescribing practices among physicians in southeastern Europe.

Keywords: Pneumonia; Cost of illness; Costs and cost analysis; Health care costs; Hospitalization; Severity of illness index.

Resumo

Objetivo: Avaliar os custos médicos diretos e indiretos de diagnóstico e tratamento para pacientes com pneumonia adquirida na comunidade (PAC), correlacionando-os com a gravidade da PAC ao diagnóstico e identificando os principais fatores de custo. **Métodos:** Análise de custos prospectiva utilizando custo *bottom-up*. A gravidade clínica e o risco de mortalidade foram determinados através de *pneumonia severity index* (PSI) e a escala *mental Confusion-Urea-Respiratory rate-Blood pressure-age ≥ 65 years* (CURB-65), respectivamente. A amostra foi composta por 95 pacientes hospitalizados devido a PAC recém-diagnosticada. A análise foi realizada em uma perspectiva social com um horizonte de tempo de um ano. **Resultados:** Expressos em média ± desvio-padrão em euros, os custos médicos diretos e indiretos por paciente com PAC foram de 696 ± 531 e 410 ± 283, respectivamente, sendo, portanto, o custo total por paciente de 1.106 ± 657. O impacto orçamentário combinado deste grupo de pacientes em euros foi de 105.087 (66.109 e 38.979 nos custos diretos e indiretos, respectivamente). Os principais fatores de custo, em ordem descendente, foram custo de oportunidade (perda de produtividade); diagnóstico e tratamento de comorbidades; e administração de medicamentos, oxigênio e derivados do sangue. Os escores CURB-65 e PSI correlacionaram-se com os custos indiretos do tratamento da PAC. O escore PSI correlacionou-se positivamente com a frequência global no uso de serviços médicos. Nenhum dos escores mostrou uma relação clara com os custos diretos do tratamento da PAC. **Conclusões:** A gravidade clínica na admissão parece não se correlacionar com os custos do tratamento da PAC. Esses custos são principalmente causados por internações hospitalares desnecessárias (ou por internação desnecessariamente prolongada) em casos de pneumonia leve, assim como pela prescrição exagerada de antibióticos. As autoridades devem se esforçar para melhorar a adesão às diretrizes e promover práticas de prescrição custo-efetivas entre os médicos do sudeste da Europa.

Descritores: Pneumonia; Efeitos psicossociais da doença; Custos e análise de custo; Custos de cuidados de saúde; Hospitalização; Índice de gravidade de doença.

Introduction

Community-acquired pneumonia (CAP) remains an ongoing challenge for health care facilities specializing in pulmonary medicine and critical care, across the globe.[1] Its treatment is still demanding, and outcomes remain unpredictable, despite the unprecedented innovation in the development of new antibiotics.[2] One major cause of the difficulties experienced in and the frequently unsatisfactory clinical outcomes of the treatment of CAP is poor adherence to clinical practice guidelines, as demonstrated in a recent study conducted in Brazil.[3] In the context of increased expectations that health care systems will deliver cost-effective care, the financial burden of CAP has attracted the attention of experts.[4] Various measures have been proposed and implemented to contain the costs related to the care of patients with CAP while preserving satisfactory clinical outcomes.[5] Among the most successful of such measures is prioritizing outpatient diagnosis and treatment over hospital admission. Commonly reported results of this strategy are lower frequency of hospital infections with multidrug-resistant bacteria and fewer resources spent on the diagnosis and treatment of associated comorbidities.[6]

In comparison with other countries in the Western Balkans, one peculiarity of Serbia, which is the largest health care market in the region, is that its health care system is rather typical of the broader Eastern European context.[7] Health expenditures continue to grow faster than the gross domestic product available among the high- and upper middle-income economies of the region.[8] The population continues to age while incidence and prevalence rates of the leading diseases common to the upper socioeconomic classes are still rising.[9] Local data regarding the financial burden of CAP remain scarce across the region.[10] Many policy makers have begun to realize that a more robust evidence base is needed in order to make informed decisions on resource allocation. In light of current weaknesses of regional health financing, funding the quest for knowledge of the local cost drivers of key clinical conditions represents a valuable investment in the future of emerging markets.[11]

Methods

This was a prospective non-interventional clinical study with retrospective insight into pneumonia-related resource use and the direct costs of medical care, as well as indirect costs associated with absenteeism and the related productivity losses. Our aim was to assess the direct and indirect costs of diagnosis and medical treatment of patients with CAP, as well as to determine whether those costs correlate with CAP severity (stage) and clinical status at diagnosis. The analysis was run from a societal perspective with a time horizon of one year, and we used bottom-up costing.

Patients were recruited from among inpatients recently diagnosed with CAP and admitted to the University of Kragujevac Center for Clinical Medicine, in Kragujevac, Serbia. The Center, which is one of several large tertiary care facilities in the country, with 1,300 beds, provides specialty care for central and western Serbia. Common clinical practice at the facility is mostly in line with current guidelines for the diagnosis and treatment of respiratory infections.[12]

We included patients ≥ 18 years of age who had received a diagnosis of CAP, confirmed by laboratory tests and imaging. A diagnosis of CAP was defined by signs of new infiltration on chest X-rays, together with at least one of the following symptoms: newly occurring cough; abnormal body temperature (< 35.6°C or > 37.5°C); and an abnormal blood cell count, defined as leukocytosis with a "left shift" or neutropenia. Patients who had a recent prior hospital admission (within the last 15 days) for any reason were excluded, as were those presenting with clinical signs indicative of pulmonary tuberculosis and those with severe pneumonia, requiring urgent admission to the intensive care unit and assisted ventilation.

Patients were enrolled consecutively over a period of 16 months. They were assessed by the attending physicians (internists who were subspecialists in pulmonology). The majority of the eligible patients (those meeting the study criteria) were recruited. Annually, there are approximately 200 hospital admissions for CAP, as well as up to 500 cases of CAP treated on an outpatient basis, at the target facility. Approximately 30% of the inpatients initially included were lost to follow up, due to loss of contact; a change of permanent residence and contact data; or voluntary withdrawal from the study.

At admission, the clinical evolution and severity of the infection were assessed with the pneumonia

severity index (PSI),[13] as well as the score on the scale known as CURB-65, an acronym based on the key terms of each risk factor evaluated (i.e., mental Confusion, Urea, Respiratory rate, Blood pressure, and age $\geq$ 65 years), which is used in order to quantify mortality risk.[14] Both of these scales are physician-oriented and have been widely adopted as reliable and valid clinical instruments. They are used worldwide to inform decisions regarding treatment, as well as to evaluate the likely prognosis.

Follow-up and observation took place from September of 2012 through December of 2013. The patient sample was representative of the population of central Serbia. Clinical background data were obtained by the attending physicians during prospective clinical follow-up. The results of a variety of laboratory tests and other diagnostic measures, as well as physical examination findings, are provided for the first and last day of hospitalization. We also determined 30-day mortality after discharge.

Patterns of resource use—frequency of physical examinations, bronchoscopies, sputum cultures, blood cultures, chest X-rays, and blood tests, as well as drug doses, etc.—were prospectively reported by the attending physicians and nurses. Direct medical costs were calculated on the basis of data available in the University of Kragujevac Center for Clinical Medicine electronic database of discharge invoices. The database contained exact prices of goods and services consumed in relation to the diagnosis and treatment of CAP. These prices were registered, at the time that the services were provided, by the primary payer, the National Health Insurance Fund of the Republic of Serbia.[15] We calculated indirect costs using Grossman's human capital approach.[16] Pneumonia caused absenteeism and resulted in opportunity costs (lost productivity), as calculated on the basis of the length of hospital stay; employment status of the patient and caregiver; and history of home care. We monetized lost work time on the basis of monthly salaries by occupation, according to the current official average values published by the Republic of Serbia.[17]

All statistical analyses were performed with the SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation, with ranges or with 95% confidence intervals. Categorical variables are presented as proportions of the sample as a whole. To test the significance of differences between pre- and post-treatment values for continuous variables, we used Student's t-tests for dependent samples or the Wilcoxon signed-rank test, depending on the normality of the data distribution (Kolmogorov-Smirnov test results). The significance of differences between two independent samples for continuous variables was measured with Student's t-tests or the Mann-Whitney U test, also depending on the normality of the data distribution. For comparisons of continuous variables among three or more groups, we used one-way ANOVA or the Kruskal-Wallis test, again depending on the normality of the data distribution. Linear correlations between key variables were tested by Spearman's and Pearson's correlation coefficients. The strength of each correlation was assessed according to Cohen's kappa ($\geq$ 0.5 = extremely strong; 0.3-0.49 = moderate; and $\leq$ 0.29 = weak). Predictors of fatal outcome were subjected to multiple logistic regression, and the results are expressed as odds ratios. The level of statistical significance was set at $p < 0.05$.

Patient data were handled in accordance with the Declaration of Helsinki and with Serbian national legislation on biomedical research in human subjects. The study was approved by the Research Ethics Committee of the University of Kragujevac Center for Clinical Medicine (Protocol no. 01-2349).

Results

The study sample was well-balanced in terms of the gender distribution, males and females respectively accounting for 46 (48.5%) and 49 (51.5%) of the 95 patients evaluated. The mean age was 63.46 $\pm$ 14.83 years (range, 23-92 years), retired individuals comprising 52.6% of the sample. The most significant risk factors were smoking and low rates of vaccination (against influenza and *Streptococcus pneumoniae*). In the vast majority of the cases, the onset of the clinical symptoms of CAP occurred at least 7 days before hospital admission (Table 1). At admission, 11 (11.6%) of the 95 patients exhibited a high degree of clinical severity (advanced stage), with impaired consciousness. The majority of patients had at least one significant comorbidity disorder, the most common comorbid condition being essential hypertension. According to the PSI scores at

admission, there was a clear predominance of class III (score range, 71-90) and class IV (score range, 91-130). On the basis of the CURB-65 scores at admission, 58 (61%) of the patients were in the low-risk group and therefore might have been candidates for outpatient treatment. Nevertheless, all of the patients in our sample were admitted to the hospital. The mean hospital stay was two weeks. Thereafter, 52 (54.7%) of the 95 patients received home care, and the mean length of follow-up treatment was approximately ten days. In most cases, home care was provided by a member of the immediate or extended family. Although most of the patients recovered fully after hospital discharge, five died during the follow-up period. On the basis of the multiple logistic regression analysis we concluded that a single determinant, the CURB-65 score, is a significant predictor of mortality (OR =12,60). All of the patients who died had been classified as

Table 1 – Baseline demographic characteristics, lifestyle risk factors, clinical severity, and mortality risk in a sample of patients hospitalized with community-acquired pneumonia in Serbia.

Variable	(N = 95)[a]
Age	63.46 ± 14.83 (23-92)
Body mass index (kg/m^2)	24.58 ± 5.36 (13.84-41.40)
Occupation	
Unknown, n (%)	19 (20)
Unemployed, n (%)	7 (7.4)
Homemaker, n (%)	3 (3.2)
Retired, n (%)	50 (52.6)
Unskilled laborer, n (%)	11 (11.6)
Health care worker, n (%)	1 (1.1)
Farmer, n (%)	1 (1.1)
Self-employed, n (%)	3 (3.2)
Nursing home occupant, n (%)	2 (2.1)
Current smoker, n (%)	44 (46.3)
Smoking history (pack-years)	
All patients	18.32 ± 22.85 (0-100)
Smokers only	37.05 ± 19.49 (0.4-100)
Previous vaccination against influenza	1 (1.1)
Previous vaccination against *Streptococcus pneumoniae*	1 (1.1)
Previous hospitalization for pneumonia, n (%)	14 (14.7)
History of alcohol consumption, n (%)	10 (10.5)
Pneumonia severity index	
Total score	85.08 ± 33.95 (13-182)
Class I (≤ 50), n (%)	15 (15.8)
Class II (51-70), n (%)	18 (18.9)
Class III (71-90), n (%)	22 (23.2)
Class IV (91-130), n (%)	32 (33.7)
Class V (> 131-395), n (%)	8 (8.4)
CURB-65 mortality risk (score)	
Low (0-1), n (%)	58 (61.1)
Moderate (2), n (%)	29 (30.5)
Severe (3-5), n (%)	8 (8.4)
Length of hospital stay (days)	14.62 ± 7.081 (3-48)
Pre-admission duration of clinical signs and symptoms of CAP (days)	6.44 ± 5.60 (1-30)
Medical care provided by a family member, n (%)	52 (54.7)
Survival at 30 days after discharge	
Yes, n (%)	90 (94.7)
No, n (%)	5 (5.3)

CURB-65: (scale based on) mental Confusion-Urea-Respiratory rate-Blood pressure-age ≥ 65 years; and CAP: community-acquired pneumonia. [a]Results presented as mean ± SD (range) except where otherwise indicated.

being in the CURB-65 moderate-risk or severe-risk group.

Most of initial laboratory and blood test results were far more concerning than were those obtained at discharge, indicating successful recovery. Clinical complications of pulmonary infection were quite common. The most common such complications were (in descending order) respiratory insufficiency, $PaO_2 < 60$ mmHg, anemia, pleural effusion, and diarrhea (Table 2).

With regards to the economics of inpatient treatment for CAP, the diagnostic tests most frequently ordered by the attending physicians at the facility under study were chest X-ray, electrocardiography, laboratory analyses (hematology and biochemistry), arterial blood gas analysis, and spirometry (see Table 3). The medications most often prescribed for the treatment of CAP, according to the mean number of defined daily doses (DDDs) per patient, were as follows: levofloxacin (8.57 DDDs); methylprednisolone (5.04 DDDs); aminophylline (4.73 DDDs); ceftriaxone (3.54 DDDs); fluticasone+salmeterol (0.73+2.20 DDDs); ceftazidime (2.47 DDDs); amikacin (2.03 DDDs); fenoterol+ipratropium bromide (0.76+1.60 DDDs); ertapenem (1.83 DDDs); and acetylcysteine (1.81 DDDs). Antibiotics were the strongest single contributor to the acquisition costs of medications.

Expressed as mean ± standard deviation (95% CI), the direct and indirect costs per CAP patient, in Euros, were 696 ± 531 (30 to 589) and 410 ± 283 (353 to 467), respectively, the total per to patient cost therefore being 1,106 ± 657 (974 to 1,238). The combined budget impact of our patient cohort was 105,087 (66,109 and 38,979 in direct and indirect costs, respectively). As can be seen in Table 4, the major cost drivers were as follows (values in Euros): general medical care (32 ± 32 [26 to 39]); administration of medications, oxygen, and blood derivatives (178 ± 211 [135 to 220]); laboratory tests and imaging (52 ± 53 [42 to 63]); consultations and surgical interventions (30 ± 38 [22 to 38]); administrative and supporting services (2 ± 20 [−2 to 6]); and the diagnosis and treatment of comorbidities (401 ± 304 [340 to 462]).

After dividing the patients into subgroups according to their CURB-65 score (mortality risk) at admission, we identified no significant cost differentials among the low-, moderate-, and severe-risk groups. Minor exceptions were oxygen and hormonal preparations, the administration of which was significantly more frequent among patients in the CURB-65 moderate- and severe-risk groups (p = 0.046 vs. the low-risk group). Paradoxically, the cost of CAP treatment was highest for the patients in the CURB-65 low-risk group. That finding can be explained by the fact that most of those cases were heavily dependent on home nursing care after early discharge, increasing the opportunity costs related to lost productivity (p = 0.002 vs. the moderate- and severe-risk groups).

There was a strong positive correlation between the PSI and CURB-65 scores (r = 0.663). We also found that the scores on the PSI and CURB-65 both correlated with the indirect costs of CAP treatment (r = −0.339 and r = −0.360, respectively). Greater CAP severity, as indicated by a higher PSI score, correlated with the use of imaging and laboratory tests (r = 0.177), as well as with the administration of medications, oxygen and blood derivatives (r = 0.257). The PSI score also correlated positively with the overall per-patient frequency of use of health care services (r = 0.354).

The overall costs of care were substantially lower for CAP non-survivors than for CAP survivors. That is primarily attributable to the shorter hospital stays among the former (p = 0.049), although the costs related to imaging, laboratory tests, physician consultations, and surgical costs were also significantly higher among the survivors (p = 0.004). Length of hospital stay exhibited strong positive correlations with direct, indirect, and total costs (r = 0.493, r = 0.307, and r = 0.531, respectively).

Discussion

The results presented here are the fruit of an attempt to analyze resource use, costs and clinical practice patterns on CAP in southeastern Europe,[10] which, to our knowledge, constitutes the first such attempt. Similar data are readily available for a number of high income economies. In Switzerland, for example, the overall cost for a single episode of CAP in a child or adolescent is calculated to be 11,258 Swiss francs, or approximately 11,000 Euros.[18] These costs vary widely among economies. In Poland, the mean cost for outpatient treatment of CAP is only 186 zlotys, or approximately 43 Euros.[19] To date, there have been only a few cost-of-illness studies on respiratory disorders in Eastern Europe, and most of those have focused on COPD, confirming its huge economic burden. Such studies have shown

Table 2 – Clinical parameters, symptoms, comorbidities, and clinical complications in a sample of patients hospitalized with community-acquired pneumonia in Serbia.

Category	Variable	(N = 95)
Clinical presentation	Body temperature (°C), mean ± SD (range)	38.19 ± 0.94 (36-40)
	Respiratory rate (breaths/min), mean ± SD (range)	19.61 ± 4.73 (12-36)
	Heart rate (bpm), mean ± SD (range)	94.45 ± 18.58 (55-150)
	Systolic blood pressure (mmHg), mean ± SD (range)	124.37 ± 19.16 (75-170)
	Diastolic blood pressure (mmHg), mean ± SD (range)	75.05 ± 10.30 (55-110)
	Cough, n (%)	80 (84.2)
	Productive cough, n (%)	49 (51.6)
	Dyspnea, n (%)	55 (57.9)
	Chest pain, n (%)	44 (46.3)
	Impaired consciousness, n (%)	11 (11.6)
	ICU admission, n (%)	9 (9.5)
	Artificial ventilation (assisted breathing), n (%)	0 (0)
Comorbid disorders	Coronary heart disease, n (%)	17 (17.9)
	Heart failure, n (%)	21 (22.1)
	Heart valves damage, n (%)	4 (4.2)
	Essential hypertension, n (%)	58(61.1)
	Asthma, n (%)	10 (10.5)
	COPD, n (%)	21 (22.1)
	Kidney failure, n (%)	11 (11.6)
	Liver failure, n (%)	2 (2.1)
	Encephalopathy, n (%)	4 (4.2)
	Diabetes mellitus, n (%)	29 (30.5)
	Cancer (any malignancy), n (%)	6 (6.3)
Clinical complications	Respiratory failure, n (%)	39 (41.1)
	$PaO_2 < 60$ mmHg, n (%)	32 (33.7)
	Pleural effusion, n (%)	23 (24.2)
	Pulmonary embolism, n (%)	1 (1.1)
	Pneumothorax, n (%)	0 (0)
	Heart failure, n (%)	17 (17.9)
	Gastrointestinal bleeding, n (%)	1 (1.1)
	Diarrhea, n (%)	21 (22.1)
	Hemoptysis, n (%)	9 (9.5)
	Empyema, n (%)	1 (1.1)
	Leukopenia, n (%)	2 (2.1)
	Anemia, n (%)	28 (29.5)
	Platelet deficiency, n (%)	2 (2.1)
	Stroke, n (%)	2 (2.1)
	Lung abscess, n (%)	3 (3.2)

that the costs of treatment increase in parallel with the degree of COPD severity, according to the Global Initiative for Chronic Obstructive Lung Disease clinical classification.[20] Intercountry comparisons of the costs of COPD treatment in Europe remain scarce, which hinders analysis of the key cost drivers and unique national health care settings.[21] Estimates of the annual economic burden of CAP have exceeded common expectations in some markets, ranging from 63 million New Zealand dollars (approximately 42 million Euros) in New Zealand to 440.7 million pounds (approximately 574 million Euros) in the United Kingdom.[21]

Our finding that the length of hospital stay had a significant impact on the overall costs of CAP treatment is supported by well-documented evidence from other national settings.[22] The strongest single cost driver in our sample was the opportunity cost related to work absenteeism.

Table 3 – Patterns of resource use and frequency of pneumonia-related clinical interventions in a sample of patients hospitalized with community-acquired pneumonia in Serbia.

Intervention	Per-patient frequency of use		Total number of examinations	Patients undergoing the examinations
	Mean ± SD	(range)		n (%)
Electrocardiography	2.92 ± 2.56	0-14	277	94 (98.9)
Bronchoscopy	0.18 ± 0.39	0-1	17	17 (17.9)
Thoracocentesis	0.09 ± 0.39	0-2	9	6 (6.4)
Thoracic drainage	0.01 ± 0.10	0-1	1	1 (1.1)
Spirometry	1.12 ± 1.47	0-7	106	52 (54.6)
Chest CT	0.27 ± 0.45	0-1	26	26 (27.4)
Chest X-ray	4.08 ± 2.42	0-20	388	95 (100)
Blood culture	0.26 ± 0.64	0-2	25	15 (15.8)
Sputum culture	0.94 ± 1.45	0-6	89	40 (42.1)
Blood workup	2.35 ± 1.16	0-8	223	93 (97.9)
Serum biochemistry	2.34 ± 1.23	0-8	222	92 (96.8)
Routine coagulation tests	0.46 ± 1.13	0-9	44	26 (27.4)
Viral immunoassays	0.07 ± 0.26	0-1	7	7 (7.4)
Blood-gas analysis	2.20 ± 3.64	0-19	209	54 (56.8)

In developed countries, such a cost matrix is common for the majority of noncommunicable diseases, although it is less common for short-term, communicable diseases. Our finding that the diagnosis and treatment of major comorbidities constituted the major cost driver could be explained by the rising incidence and financial burden of diseases common to the upper socioeconomic classes in Eastern Europe. Local evidence strongly supporting our findings can be found in other studies, also conducted in Serbia, evaluating the burdens of diabetes mellitus, COPD, addiction, fertility disorders, hepatitis, and cancer.[23-27]

Our data, which were acquired in a prospective manner within a methodologically appropriate framework, show that only the PSI score was predictive of the volume of health care services consumed. The CURB-65 and PSI scores both showed a satisfactory positive predictive value for the opportunity costs related to lost productivity. Nevertheless, we failed to identify any significant correlations between either of those clinical assessments of severity and the direct costs of CAP treatment. The lack of any such correlation is likely the result of poor physician adherence to guidelines.[28] It seems that high prescription rates and the overuse of diagnostics measures (imaging and laboratory testing) are common in cases of CAP that are treated in the early, mild stages. Resource use and costs in more severe, advanced cases of CAP, in which the outcome is highly unpredictable, too frequently approach those seen in mild cases. It is likely that this is primarily

attributable to long hospital stays, the routine administration of multiple antibiotics, and the use of the expensive parenteral medications preferred by physicians in the region. An excellent recent example of how adherence to clinical guidelines can downsize treatment expenditures and generate savings was provided in a controlled study of alcohol addiction conducted by our group.[29] Our findings in the present study underscore the need for health care policies establishing stricter supervision of standard clinical practice. Analysis of the current state of the art of CAP treatment in Serbia, the largest health care market in the Western Balkans, indicates that the allocation of resources is inefficient. Providing local physicians with better evidence-based guidelines on cost-effective medical interventions for pneumonia would likely improve clinical outcomes and generate savings.

The present study has some minor limitations. Conducting a prospective cost-of-illness study in parallel with a non-interventional clinical study in one large university hospital precludes a substantial increase in the sample size. A multicenter study conducted across several countries in the region might allow the knowledge of CAP treatment costs to be expanded beyond its current limits. Unfortunately, such an additional effort was not within the scope of the present study. Nevertheless, the results of our study, which we believe to be the first of its kind conducted in southeastern Europe, could lay the groundwork for improved

Table 4 – Cost matrix of medical care for community-acquired pneumonia, including cost per patient and total expenditures, in a sample of patients hospitalized with community-acquired pneumonia in Serbia, 2012-2013.

Variable	Per patient cost, in Euros[a] Mean ± SD (range)	Total cost, in Euros
General medical care	32 ± 32 (26 to 39)	3,086
Nursing care	12.1 ± 12.2 (9.6 to 14.5)	1,147
Consumables	20.4 ± 21.0 (16.2 to 24.6)	1,939
Medications, oxygen, blood, and blood derivatives	178 ± 211 (135 to 220)	16,894
Anti-infective medicines for systemic use	165.4 ± 199.1 (125.3 to 205.4)	15,710
Blood and blood derivatives	1.1 ± 10.5 (−1.0 to 3.2)	103
Antiseptics and disinfectants	0.3 ± 0.4 (0.3 to 0.4)	31
Cholesterol-lowering drugs (statins, fibrates, etc.) and dietary supplements (vitamins and minerals)	0.2 ± 1.0 (0.0 to 0.4)	21
Oxygen and systemic hormonal preparations (insulin, bisphosphonates, steroids, etc.)	10.8 ± 22.7 (6.3 to 15.4)	1,029
Laboratory analysis and imaging diagnostics	52 ± 53 (42 to 63)	4,989
Laboratory analysis	29.8 ± 29.8 (23.9 to 35.8)	2,836
Simple X-rays	3.4 ± 2.7 (2.9 to 4.4)	327
Nuclear medicine diagnostics	0.3 ± 1.9 (−0.1 to 0.6)	26
Tools and consumables	0.1 ± 0.5 (0.0 to 0.2)	7
Cardiovascular interventional radiology	12.3 ± 35.6 (5.2 to 19.5)	1,173
Tools and consumables	0.4 ± 4.1 (−0.4 to 1.2)	40
Contrast agents, film, etc., for radiological services	6.1 ± 8.8 (4.3 to 7.9)	581
Consultations and surgical interventions	30 ± 38 (22 to 38)	2,858
Consultations	28.7 ± 37.3 (21.3 to 36.2)	2,731
Surgical interventions	0.9 ± 3.9 (0.2 to 1.7)	90
Dialysis and psychiatric treatment	0.4 ± 1.4 (0.1 to 0.7)	37
Administrative and supporting services	2 ± 20 (−2 to 6)	192
Diagnosis and treatment of comorbidities	401 ± 304 (340 to 462)	38,092
Direct costs	696 ± 531 (30 to 589)	66,109
Indirect costs	410 ± 283 (353 to 467)	38,979
Total costs	1,106 ± 657 (974 to 1,238)	105,087

cost-efficiency in the treatment of pneumonia in the region.

As previously mentioned, the dominant cost drivers were the treatment of comorbid disorders, clinical complications, and the opportunity cost related to lost productivity. In view of the high incidence of respiratory infections in European communities, health care authorities should strive to improve adherence to guidelines and promote cost-effective prescribing practices among physicians in the region. Adopting long-term strategies aimed at reshaping the mindset of regional hospital staff would help contain costs and improve clinical outcomes.

References

1. Polverino E, Torres MA. Community-acquired pneumonia. Minerva Anestesiol. 2011;77(2):196-211.

2. Garre M, Potard M, Hiar I, Tonnelier JM, Gentric A. Antimicrobial therapy of community-acquired pneumonia. New antibiotics, abbreviated course treatment, cost-benefit analysis. Med Mal Infect. 2001;31(4):174-80.

3. Silveira CD, Ferreira CS, Corrêa Rde A. Adherence to guidelines and its impact on outcomes in patients hospitalized with community-acquired pneumonia at a university hospital. J Bras Pneumol. 2012;38(2):148-57.

4. Zhou QT, He B, Zhu H. Potential for cost-savings in the care of hospitalized low-risk community-acquired pneumonia patients in China. Value Health. 2009;12(1):40-6. http://dx.doi.org/10.1111/j.1524-4733.2008.00410.x

5. Hoe LK, Keang LT. Hospitalized low-risk community-acquired pneumonia: outcome and potential for cost-savings. Respirology. 1999;4(3):307-9. http://dx.doi.org/10.1046/j.1440-1843.1999.00197.x

6. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44, Suppl 2:S27-72 http://dx.doi.org/10.1086/511159

7. Jakovljevic MB. Resource allocation strategies in Southeastern European health policy. Eur J Health

Econ. 2013;14(2):153-9. http://dx.doi.org/10.1007/s10198-012-0439-y

8. Jakovljevic MB. Health Expenditure Dynamics in Serbia 1995-2012. Hospital Pharmacology. 2014;1(3):180-3.

9. Jakovljevic M, Jovanovic M, Lazic Z, Jakovljevic V, Djukic A, Velickovic R, et al. Current efforts and proposals to reduce healthcare costs in Serbia. Ser J Exp Clin Res. 2011;12 (4):161-3. http://dx.doi.org/10.5937/sjecr1104161J

10. Jakovljevic M, Cupurdija V, Lazic Z. Cost of illness of community-acquired pneumonia. Review of the literature and possible strategies in the Serbian health care setting. Farmeconomia. Health economics and therapeutic pathways. 2013;14(4):133-9.

11. Jakovljevic MB. The key role of leading emerging BRIC markets for the future of global health care. Ser J Exp Clin Res. 2014;15(3):139-43. http://dx.doi.org/10.5937/sjecr1403139J

12. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Eur Respir J. 2011;17 Suppl 6:E1-59.

13. Valencia M, Badia JR, Cavalcanti M, Ferrer M, Agustí C, Angrill J, et al. Pneumonia severity index class V patients with community-acquired pneumonia: characteristics, outcomes, and value of severity scores. Chest. 2007;132(2):515-22. http://dx.doi.org/10.1378/chest.07-0306

14. Richards G, Levy H, Laterre PF, Feldman C, Woodward B, Bates BM, et al. CURB-65, PSI, and APACHE II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS. J Intensive Care Med. 2011;26(1):34-40. http://dx.doi.org/10.1177/0885066610383949

15. National Health Insurance Fund [homepage on the Internet]. Belgrade: Republic of Serbia [cited 2014 Aug 1]. Available from: http://www.eng.rfzo.rs/index.php/about-us/about-us

16. Zweifel P. The Grossman model after 40 years. Eur J Health Econ. 2012;13(6):677-82. http://dx.doi.org/10.1007/s10198-012-0420-9

17. Trading Economics [homepage on the Internet]. New York/Lisbon: Trading Economics [cited 2014 Aug 1]. Serbia Wages 2000-2015. Available from: http://www.tradingeconomics.com/serbia/wages.

18. Keitel K, Alcoba G, Lacroix L, Manzano S, Galetto-Lacour A, Gervaix A. Observed costs and health care use of children in a prospective cohort study on community-acquired pneumonia in Geneva, Switzerland. Swiss Med Wkly. 2014;144:w13925.

19. Jahnz-Rózyk K. Health economic impact of viral respiratory infections and pneumonia diseases on the elderly population in Poland. Pol Merkur Lekarski. 2010;29(169):37-40.

20. Lazic Z, Gajovic O, Tanaskovic I, Milovanovic D, Atanasijevic D, Jakovljevic M. GOLD Stage Impact on COPD Direct Medical Costs in Elderly. J Health Behav & Pub Health. 2012;2(3):1-7.

21. Jakovljevic M, Lazic Z, Verhaeghe N, Jankovic S, Gajovic O, Annemans L. Direct medical costs of COPD diagnosis and treatment, Eastern vs. Western European country--examples of Serbia and Belgium. Farmeconomia. Health economics and therapeutic pathways 2013;14(4):161-8.

22. Fine MJ, Pratt HM, Obrosky DS, Lave JR, McIntosh LJ, Singer DE, et al. Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. Am J Med. 2000;109(5):378-85. http://dx.doi.org/10.1016/S0002-9343(00)00500-3

23. Biorac N, Jakovljevic MB, Stefanovic D, Perovic S, Jankovic S. Assessment of diabetes mellitus type 2 treatment costs in the Republic of Serbia. [Article in Serbian]. Vojnosanit Pregl. 2009;66(4):271-6. http://dx.doi.org/10.2298/VSP0904271B

24. Jovanovic M, Jakovljevic M. Inpatient detoxification procedure and facilities: financing considerations from an Eastern European perspective. Alcohol Alcohol. 2011;46(3):364-5. http://dx.doi.org/10.1093/alcalc/agr010

25. Jakovljevic M, Varjacic M, Jankovic SM. Cost-effectiveness of ritodrine and fenoterol for treatment of preterm labor in a low-middle-income country: a case study. Value Health. 2008;11(2):149-53. http://dx.doi.org/10.1111/j.1524-4733.2007.00222.x

26. Jakovljevic M, Mijailovic Z, Jovicic BP, Canovic P, Gajovic O, Jovanovic M, et al. Assessment of viral genotype impact to the cost-effectiveness and overall costs of care for PEG-interferon-2α + ribavirine treated chronic hepatitis C patients. Hepat Mon. 2013;13(6):e6750.

27. Jakovljevic MB. Oncology monoclonal antibodies expenditure trends and reimbursement projections in the emerging Balkan market. Farmeconomia. Health economics and therapeutic pathways. 2014;15(1):27-32.

28. Conterno LO, Moraes FY, Silva Filho CR. Implementation of community-acquired pneumonia guidelines at a public hospital in Brazil. J Bras Pneumol. 2011;37(2):152-9. http://dx.doi.org/10.1590/S1806-37132011000200004

29. Jakovljevic M, Jovanovic M, Rancic N, Vyssoki B, Djordjevic N. LAT Software Induced Savings on Medical Costs of Alcohol Addicts' Care--Results from a Matched-Pairs Case-Control Study. PLoS One. 2014;9(11):e111931. http://dx.doi.org/10.1371/journal.pone.0111931

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Diagnostic accuracy of the Bedside Lung Ultrasound in Emergency protocol for the diagnosis of acute respiratory failure in spontaneously breathing patients*,**

Acurácia diagnóstica do protocolo de ultrassom pulmonar à beira do leito em situações de emergência para diagnóstico de insuficiência respiratória aguda em pacientes com ventilação espontânea

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Abstract

Objective: Bedside lung ultrasound (LUS) is a noninvasive, readily available imaging modality that can complement clinical evaluation. The Bedside Lung Ultrasound in Emergency (BLUE) protocol has demonstrated a high diagnostic accuracy in patients with acute respiratory failure (ARF). Recently, bedside LUS has been added to the medical training program of our ICU. The aim of this study was to investigate the accuracy of LUS based on the BLUE protocol, when performed by physicians who are not ultrasound experts, to guide the diagnosis of ARF. **Methods:** Over a one-year period, all spontaneously breathing adult patients consecutively admitted to the ICU for ARF were prospectively included. After training, 4 non-ultrasound experts performed LUS within 20 minutes of patient admission. They were blinded to patient medical history. LUS diagnosis was compared with the final clinical diagnosis made by the ICU team before patients were discharged from the ICU (gold standard). **Results:** Thirty-seven patients were included in the analysis (mean age, 73.2 ± 14.7 years; APACHE II, 19.2 ± 7.3). LUS diagnosis had a good agreement with the final diagnosis in 84% of patients (overall kappa, 0.81). The most common etiologies for ARF were pneumonia (n = 17) and hemodynamic lung edema (n = 15). The sensitivity and specificity of LUS as measured against the final diagnosis were, respectively, 88% and 90% for pneumonia and 86% and 87% for hemodynamic lung edema. **Conclusions:** LUS based on the BLUE protocol was reproducible by physicians who are not ultrasound experts and accurate for the diagnosis of pneumonia and hemodynamic lung edema.

Keywords: Ultrasonography, interventional; Respiratory insufficiency; Intensive care units.

Resumo

Objetivo: O ultrassom pulmonar (USP) à beira do leito é uma técnica de imagem não invasiva e prontamente disponível que pode complementar a avaliação clínica. O protocolo *Bedside Lung Ultrasound in Emergency* (BLUE, ultrassom pulmonar à beira do leito em situações de emergência) demonstrou elevado rendimento diagnóstico em pacientes com insuficiência respiratória aguda (IRpA). Recentemente, um programa de treinamento em USP à beira do leito foi implementado na nossa UTI. O objetivo deste estudo foi avaliar a acurácia do USP baseado no protocolo BLUE, quando realizado por médicos com habilidades básicas em ultrassonografia, para orientar o diagnóstico de IRpA. **Métodos:** Ao longo de um ano, todos os pacientes adultos consecutivos respirando espontaneamente admitidos na UTI por IRpA foram prospectivamente inclusos. Após treinamento, 4 operadores com habilidades básicas em ultrassonografia realizaram o USP em até 20 minutos após a admissão na UTI, cegados para a história do paciente. Os diagnósticos do USP foram comparados aos diagnósticos da equipe assistente ao final da internação na UTI (padrão-ouro). **Resultados:** Foram inclusos na análise 37 pacientes (média etária: 73,2 ± 14,7 anos; APACHE II: 19,2 ± 7,3). O diagnóstico do USP demonstrou concordância com o diagnóstico final em 84% dos casos (kappa total: 0,81). As causas mais comuns de IRpA foram pneumonia (n = 17) e edema pulmonar cardiogênico (n = 15). A sensibilidade e a especificidade do USP comparado ao diagnóstico final foram de 88% e 90% para pneumonia e de 86% e 87% para edema pulmonar cardiogênico, respectivamente. **Conclusões:** O USP baseado no protocolo BLUE foi reproduzível por médicos com habilidades básicas em ultrassonografia e acurado para o diagnóstico de pneumonia e de edema pulmonar cardiogênico.

Descritores: Ultrassonografia de intervenção; Insuficiência respiratória; Unidades de terapia intensiva.

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Introduction

Acute respiratory failure (ARF) is a critical condition requiring dynamic evaluation and interventions. Bedside lung ultrasound (LUS) is a noninvasive, readily available imaging modality that can complement physical examination and clinical evaluation.[1,2] The main advantage of bedside LUS is its immediate application to the diagnosis of thoracic disorders. Other advantages include delaying or even avoiding the need for patient transportation to the radiology suite or for radiation exposure and guiding life-saving therapies in extreme emergency.[1,3-5] The use of LUS by emergency physicians, intensivists, and pulmonologists has been reported in many studies.[1,4-10]

The appeal for using LUS in ARF patients is evident since LUS can detect lung aeration changes in many life-threatening conditions, such as acute lung edema, acute respiratory distress syndrome, pneumonia, and pneumothorax.[4-6,10-14] Recently, Lichtenstein and colleagues proposed a diagnostic algorithm—the Bedside Lung Ultrasound in Emergency (BLUE) protocol—to guide the diagnosis of severe dyspnea.[15] The authors showed that the diagnostic accuracy of LUS, as measured against the final diagnosis made by the Intensive Care Unit (ICU) team, was 90.5%. Similarly, Silva et al. demonstrated that the diagnostic accuracy of the LUS approach in ARF patients was higher than was that of an initial routine evaluation based on clinical, radiological, and biological data (83% vs. 63%, p < 0.02).[16]

Since ultrasound is an operator-dependent imaging modality and bedside LUS is a recently developed tool, the reproducibility of findings obtained by physicians who are not ultrasound experts needs further validation. Indeed, the original BLUE protocol was performed by highly qualified ultrasound experts.[15] Recently, ultrasound training has been added to the medical training program in our ICU. As we were concerned about the accuracy of bedside LUS performed by physicians who are not ultrasound experts, we therefore decided to investigate the diagnostic accuracy of the BLUE protocol for ARF.

Methods

Patients

We conducted a prospective study of all spontaneously breathing adult patients consecutively admitted to our 23-bed clinical-surgical ICU for ARF. This research was approved by the institutional ethics committee (Protocol no. 112/2011), which waived the requirement for informed consent.

The inclusion criteria were age ≥ 18 years and admission to the ICU for ARF, defined by one of the following: a respiratory rate ≥ 30 breaths/min; a PaO_2 ≤ 60 mmHg; an oxygen saturation on room air ≤ 90%, as measured by pulse oximetry; or a carbon dioxide tension (PCO_2) ≥ 45 mmHg with an arterial pH ≤ 7.35. The exclusion criteria were having required intubation before admission and/or having a multiple diagnosis or a rare (i.e., frequency < 2%) diagnosis, according to the original protocol.[15]

Study design and LUS assessment

After attending 5 hours of theoretical training and performing 10 supervised LUS examinations, 4 non-ultrasound experts participated in the study. They were blinded to patient medical history and were not involved in diagnostic or therapeutic decisions. All patients were placed in a semirecumbent position and were evaluated with the same curvilinear probe with a range of 3-5 MHz (Toshiba Tosbee®; Toshiba, Tokyo, Japan). As a rule, LUS was performed within 20 minutes of admission, by one non-ultrasound expert. Each patient underwent a bedside chest X-ray at admission, which was interpreted by a radiologist unblinded to medical history. The initial clinical evaluation and diagnosis were performed by the physicians responsible for patient care. They were blinded to the LUS results but were aware of the chest X-ray results. The final diagnosis of the episode of ARF made by the ICU team before patients were discharged from the ICU was considered the gold standard. The main diagnoses, including pneumonia, acute hemodynamic lung edema, obstructive lung disease (i.e., decompensated COPD or asthma), and pneumothorax, were evaluated. Patients with a multiple diagnosis or rare diseases were excluded from the analysis, as in the original BLUE protocol study.[15]

LUS images were recorded for each of six quadrants in each hemithorax (upper and lower parts of the anterior, lateral, and posterior chest wall, delimited by anterior and posterior axillary lines).[3,15] Each quadrant was classified on the basis of worst findings into categories according

to the predominant profile (A, B, or C) in each hemithorax, as previously described.[5,15]

The A, B, and C profiles were defined as follows (Figure 1):

- A profile (A-lines): white (hyperechoic) horizontal lines that are static and appear at regular intervals.
- B profile (B-lines): hyperechoic vertical artifacts that move in synchrony with the respiratory cycle.
- C profile: consolidation image appearing as a tissue structure containing white points consisting of lung parenchyma.

To identify normal lung aeration, lung sliding is a key ultrasound finding. It corresponds to the regular movement of the pleural line (described as a shimmering or bright white line) in regular cycles in synchrony with each respiratory movement.

In accordance with the BLUE protocol (Table 1),[15] a normal profile (bilateral lung sliding with A-lines) should be combined with screening for leg vein thrombosis. Deep venous thrombosis was sought using the same probe. A positive finding was the visualization of anatomic echoic intraluminal thrombosis or the absence of compression of femoral or popliteal veins. If there were signs of leg vein thrombosis, pulmonary embolism was the diagnosis; otherwise, the normal pattern was suggestive of respiratory dysfunction due to obstructive lung disease (i.e., decompensated COPD or asthma).[3,5,15] The absence of lung sliding combined with the presence of A-lines was suggestive of pneumothorax. However, for this diagnosis, it was necessary to identify the lung point (the point where it is possible to identify both normal lung sliding and its absence).[3,5,15] Also, the identification of a normal anterior pattern associated with the presence of pleural effusion and posterior consolidation (A profile with posterior alveolar syndrome, pleural syndrome, or both) or an anterior or lateral consolidation (C profile) was suggestive of pneumonia.[3,15,16]
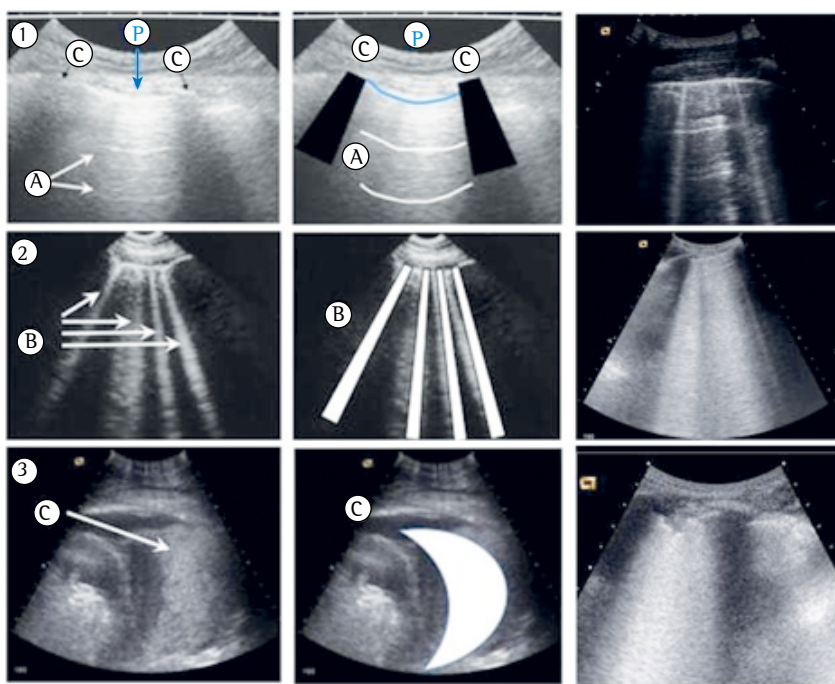
Adapted from Dexheimer Neto et al.[9]

Figure 1 – Lung ultrasound findings (left), their schematic representation (center), and illustrative examples (right). P: pleural line; c: ribs; A: A-lines; B: B-lines; and C: pulmonary consolidation.
- Panel 1: Normal lung aeration – A profile (A-lines): white (hyperechoic) horizontal lines that are static and appear at regular intervals.
- Panel 2: Partial loss of lung aeration – B Profile (B-lines): hyperechoic vertical artifacts that move in synchrony with the respiratory cycle.
- Panel 3: Total loss of lung aeration – C profile (consolidation): consolidation image appearing as a tissue structure containing white points consisting of lung parenchyma.

Table 1 – Lung ultrasound profiles in acute respiratory failure.

Condition	Lung ultrasound finding
Pneumonia	AB profile, or consolidation, or A profile with posterior alveolar syndrome, pleural syndrome, or both
Acute hemodynamic lung edema	B profile
Obstructive lung disease (i.e., decompensated COPD or asthma)	A profile without DVT
Pneumothorax	A profile with a lung point and no lung sliding
Pulmonary embolism	A profile with DVT

DVT: deep vein thrombosis.

A B profile characterized by symmetric bilateral B-lines suggested hemodynamic lung edema.[3,9,15] However, B-line predominance without lung sliding could also be suggestive of pneumonia.

The AB profile was characterized by asymmetric findings between the hemithoraces, suggestive of pulmonary infection as the etiology of ARF.

Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous data are expressed as mean ± standard deviation. The diagnostic performance of LUS as measured against each final diagnosis was assessed by calculation of sensitivity, specificity, and predictive values by using a standard formula. The completeness and accuracy of reporting was assessed with the Standards of Reporting of Diagnostic Accuracy checklist.[17] In addition, the level of agreement among observers for the ultrasound findings and the final clinical diagnosis was evaluated with the kappa reliability test: kappa values < 0 indicated less than chance agreement; kappa values of 0.01-0.20 indicated slight agreement; kappa values of 0.21-0.40 indicated fair agreement; kappa values of 0.41-0.60 indicated moderate agreement; kappa values of 0.61-0.80 indicated substantial agreement; and kappa values of 0.81-0.99 indicated almost perfect agreement.[18] McNemar's test was used to compare within-subject diagnostic accuracy between LUS and chest X-ray and between LUS and the initial clinical evaluation. Statistical analysis was performed with IBM-SPSS software, version 16 (IBM Inc., Armonk, NY, USA). All tests were two-tailed, and a p value < 0.05 was considered statistically significant.

Results

Forty-two consecutive patients admitted to the ICU for ARF between October of 2011 and November of 2012 were enrolled in the study. As previously described, 5 patients with rare diagnoses were excluded from the final analysis (2 patients with pulmonary fibrosis, 1 patient with hypersensitivity pneumonitis, 1 with leptospirosis, and 1 with abdominal compartment syndrome). The baseline characteristics of the patients are shown in Table 2.

Of the 37 medical patients, 70% were transferred from the medical ward. The mean hospital length of stay before ICU admission was 7.9 ± 7.7 days. Noninvasive or invasive positive-pressure ventilation was required in 92% of the patients (Table 2). The overall observed mortality was 42%.

According to the final diagnosis, the most common etiology of ARF was pneumonia (n = 17). Fifteen patients were admitted for hemodynamic lung edema, and 4 were admitted for obstructive lung disease. There was only one patient with pulmonary embolism (in this patient, LUS was normal as expected, but it was not possible to identify deep vein thrombosis) and none with pneumothorax. The sensibility, specificity, and predictive values are shown in Table 3. Pulmonary embolism and pneumothorax were not included because the number of patients with these conditions was insufficient to perform diagnostic performance analysis.

The BLUE protocol diagnosis made at admission by physicians who are not ultrasound experts had a perfect agreement with the final diagnosis in 84% of the patients (overall kappa, 0.81). Agreements between the 2 methods were 0.78 and 0.74 for pneumonia and lung edema, respectively.

The diagnostic accuracy of LUS alone was significantly higher than was that of chest X-ray alone (84% vs. 43%; p = 0.01). No significant difference was found between LUS and the standard initial clinical evaluation (84% vs. 65%; p = 0.12).

Discussion

The main result of the present study is that bedside LUS performed by physicians who are not ultrasound experts allows the correct diagnosis of the most common causes of ARF (pneumonia and hemodynamic lung edema) with good sensitivity and specificity, as measured against the final diagnosis. The high overall diagnostic accuracy of LUS (84%) and the good agreement (kappa coefficient, 0.81) between LUS and the final diagnosis confirmed the high diagnostic yield of LUS. Indeed, the diagnostic accuracy of LUS was higher than was that of chest X-ray.

The primary concern that led us to perform the present study was operator bias, since different operators could interpret ultrasonographic patterns of lung differently. Gaining competence in a skill over time is a well-recognized process,

which has also been demonstrated for LUS.[19] In most previous studies, a limited number of investigators who were experts in LUS performed the ultrasound examinations.[10,15,16] Lichtenstein et al. reported a sensitivity and a specificity of 97% and 95%, respectively, for hemodynamic lung edema and of 94% and 89%, respectively, for pneumonia.[15] In our study, the values obtained by physicians who are not ultrasound experts, although slightly lower (86% and 87%, respectively, for lung edema, and 88% and 90%, respectively, for pneumonia), are close to those reported by expert physicians.[10,15] This result indicates that the BLUE protocol is feasible and reproducible.

Recently, Silva et al. compared the accuracy of cardiothoracic ultrasound with that of an initial clinical evaluation, as measured against the final diagnosis made by an expert panel, in 78 ARF patients.[16] The authors found that the ultrasound approach was significantly more accurate than was the initial clinical approach (83% vs. 63%, respectively; p < 0.02). This finding indicates that the use of LUS data could have significantly improved the initial diagnosis.[16] Similarly, it has been shown that therapeutic management can be changed directly as a result of information provided by LUS in up to 47% of mechanically ventilated patients.[20] Interestingly, our results show similar accuracy rates, with accuracy being higher for LUS than for the initial clinical evaluation (84% vs. 65%).[16] However, our study was underpowered to find a significant difference.

In this study, LUS accuracy was significantly higher than was that of chest X-ray (84% vs. 43%; p = 0.009). Indeed, bedside LUS has been shown to have superior accuracy when evaluating patients with atelectasis, pneumothorax, pneumonia, or acute respiratory distress syndrome, compared with chest X-ray.[2,4,9,14,21]

In an attempt to increase concordance, all patients were evaluated in the same position and with the same probe. There is no recommendation for the duration of LUS training.[22-24] In the present study, in order to homogenize the interpretation of LUS findings, we arbitrarily

Table 2 – Characteristics of the patients admitted to the ICU for acute respiratory failure (n = 37).[a]

Characteristic	Result
Age, years	73.2 ± 14.7
Male gender	16 (43)
BMI	25.7 ± 4.7
APACHE II score	19.2 ± 7.3
Glasgow Coma score	12.7 ± 3.1
pH	7.32 ± 0.13
PaO_2/FiO_2	173.15 ± 108.2
PCO_2	50.9 ± 48
Previous diseases:	
Cancer	11 (30)
Heart disease	22 (59)
Heart Failure	7 (19)
Obstructive lung disease	8 (22)
Neurological disease	7 (19)
Chronic renal failure	4 (11)
Immediate trial of NIV	15 (41)
Success of NIV	6 (16)
Orotracheal intubation at admission (without a previous NIV trial)	19 (51)
Spontaneous breathing	3 (8)

BMI: body mass index; APACHE: Acute Physiological and Chronic Health Evaluation; PCO_2: carbon dioxide tension; and NIV: noninvasive ventilation. [a]Data expressed as mean ± SD or n (%).

Table 3 – Diagnostic performance of bedside lung ultrasound for each diagnosis.

Diagnosis	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Pneumonia (n = 17)	88%	90%	88%	90%
Hemodynamic lung edema (n = 15)	85%	87%	80%	91%
Obstructive lung disease (n = 4)	67%	100%	100%	94%

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chose a total of 5 hours of theoretical training and 10 supervised ultrasound examinations. With this training method, our operators were able to individually achieve substantial diagnostic agreement (kappa coefficient, 0.81).

Bedside LUS is rapidly becoming integral to the evaluation of critically ill patients. However, it is still not widely used in Brazil. Costs are often regarded as major barriers.[22] In a study conducted in Italy, the use of bedside LUS was associated with a 26% reduction in the total number of chest X-rays and a 47% reduction in the total number of CT scans.[25]

The main limitations of this study are its small sample size and the fact that it was conducted in a single center. Because our results are based mainly on the diagnoses of pneumonia and hemodynamic lung edema, further studies are needed to validate the BLUE protocol in the diagnosis of other causes of ARF. In addition, intra- and inter-operator variabilities were not assessed. Furthermore, as we followed the original BLUE protocol, our study did not incorporate the diagnosis of pleural effusion as an etiology of ARF, although LUS has great potential in the diagnosis of this pattern.[5]

In conclusion, this study, conducted in an ICU in Brazil, has demonstrated that the BLUE protocol is feasible and can easily be implemented in the ICU. After a brief training period, physicians are able to diagnose the main causes of ARF with accuracy.

Acknowledgments

References

1. Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. Chest. 2011;140(5):1332-41. http://dx.doi.org/10.1378/chest.11-0348

2. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. Anesthesiology. 2004;100(1):9-15. http://dx.doi.org/10.1097/00000542-200401000-00006

3. Bouhemad B, Zhang M, Lu Q, Rouby JJ. Clinical review: Bedside lung ultrasound in critical care practice. Crit Care. 2007;11(1):205. http://dx.doi.org/10.1186/cc5668

4. Manno E, Navarra M, Faccio L, Motevallian M, Bertolaccini L, Mfochivè A, et al. Deep impact of ultrasound in the intensive care unit: the "ICU-sound" protocol.

Anesthesiology. 2012;117(4):801-9. http://dx.doi.org/10.1097/ALN.0b013e318264c621

5. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38(4):577-91. http://dx.doi.org/10.1007/s00134-012-2513-4

6. Bouhemad B, Liu ZH, Arbelot C, Zhang M, Ferarri F, Le-Guen M, et al. Ultrasound assessment of antibiotic-induced pulmonary reaeration in ventilator-associated pneumonia. Crit Care Med. 2010;38(1):84-92. http://dx.doi.org/10.1097/CCM.0b013e3181b08cdb

7. Remérand F, Dellamonica J, Mao Z, Ferrari F, Bouhemad B, Jianxin Y, et al. Multiplane ultrasound approach to quantify pleural effusion at the bedside. Intensive Care Med. 2010;36(4):656-64. http://dx.doi.org/10.1007/s00134-010-1769-9

8. Soummer A, Perbet S, Brisson H, Arbelot C, Constantin JM, Lu Q, et al. Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress*. Crit Care Med. 2012;40(7):2064-72. http://dx.doi.org/10.1097/CCM.0b013e31824e68ae

9. Dexheimer Neto FL, Dalcin Pde T, Teixeira C, Beltrami FG. Lung ultrasound in critically ill patients: a new diagnostic tool. J Bras Pneumol. 2012;38(2):246-56. http://dx.doi.org/10.1590/S1806-37132012000200015

10. Chavez MA, Shams N, Ellington LE, Naithani N, Gilman RH, Steinhoff MC, et al. Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis. Respir Res. 2014;15:50. http://dx.doi.org/10.1186/1465-9921-15-50

11. Bouhemad B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. Am J Respir Crit Care Med. 2011;183(3):341-7. http://dx.doi.org/10.1164/rccm.201003-0369OC

12. Caltabeloti FP, Monsel A, Arbelot C, Brisson H, Lu Q, Gu WJ, et al. Early fluid loading in acute respiratory distress syndrome with septic shock deteriorates lung aeration without impairing arterial oxygenation: a lung ultrasound observational study. Crit Care. 2014;18(3):R91. http://dx.doi.org/10.1186/cc13859

13. Baldi G, Gargani L, Abramo A, D'Errico L, Caramella D, Picano E, et al. Lung water assessment by lung ultrasonography in intensive care: a pilot study. Intensive Care Med. 2013;39(1):74-84. http://dx.doi.org/10.1007/s00134-012-2694-x

14. Ding W, Shen Y, Yang J, He X, Zhang M. Diagnosis of pneumothorax by radiography and ultrasonography: a meta-analysis. Chest. 2011;140(4):859-66. http://dx.doi.org/10.1378/chest.10-2946

15. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 2008;134(1):117-25. http://dx.doi.org/10.1378/chest.07-2800

16. Silva S, Biendel C, Ruiz J, Olivier M, Bataille B, Geeraerts T, et al. Usefulness of cardiothoracic chest ultrasound in the management of acute respiratory failure in critical care practice. Chest. 2013;144(3):859-65. http://dx.doi.org/10.1378/chest.13-0167

17. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ. 2003;326(7379):41-4. http://dx.doi.org/10.1136/bmj.326.7379.41

18. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005;37(5):360-3.

19. Tutino L, Cianchi G, Barbani F, Batacchi S, Cammelli R, Peris A. Time needed to achieve completeness and accuracy in bedside lung ultrasound reporting in intensive care unit. Scand J Trauma Resusc Emerg Med. 2010;18:44. http://dx.doi.org/10.1186/1757-7241-18-44

20. Xirouchaki N, Georgopoulos D. Impact of lung ultrasound on clinical decision making in critically ill patients: response to O'Connor et al. Intensive Care Med. 2014;40(7):1063. http://dx.doi.org/10.1007/s00134-014-3316-6

21. Cortellaro F, Colombo S, Coen D, Duca PG. Lung ultrasound is an accurate diagnostic tool for the diagnosis of pneumonia in the emergency department. Emerg Med J. 2012;29(1):19-23. http://dx.doi.org/10.1136/emj.2010.101584

22. Bahner DP, Adkins EJ, Hughes D, Barrie M, Boulger CT, Royall NA. Integrated medical school ultrasound: development of an ultrasound vertical curriculum. Crit Ultrasound J. 2013;5(1):6. http://dx.doi.org/10.1186/2036-7902-5-6

23. Mosier JM, Malo J, Stolz LA, Bloom JW, Reyes NA, Snyder LS, et al. Critical care ultrasound training: a survey of US fellowship directors. J Crit Care. 2014;29(4):645-9. http://dx.doi.org/10.1016/j.jcrc.2014.03.006

24. Noble VE, Lamhaut L, Capp R, Bosson N, Liteplo A, Marx JS, et al. Evaluation of a thoracic ultrasound training module for the detection of pneumothorax and pulmonary edema by prehospital physician care providers. BMC Med Educ. 2009;9:3. http://dx.doi.org/10.1186/1472-6920-9-3

25. Peris A, Tutino L, Zagli G, Batacchi S, Cianchi G, Spina R, et al. The use of point-of-care bedside lung ultrasound significantly reduces the number of radiographs and computed tomography scans in critically ill patients. Anesth Analg. 2010;111(3):687-92. http://dx.doi.org/10.1213/ANE.0b013e3181e7cc42

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Chronic rhinosinusitis and nasal polyposis in cystic fibrosis: update on diagnosis and treatment*

Rinossinusite crônica e polipose nasossinusal na fibrose cística: atualização sobre diagnóstico e tratamento

Suzie Hyeona Kang, Paulo de Tarso Roth Dalcin, Otavio Bejzman Piltcher, Raphaella de Oliveira Migliavacca

Abstract

Although cystic fibrosis (CF) is an irreversible genetic disease, advances in treatment have increased the life expectancy of CF patients. Upper airway involvement, which is mainly due to pathological changes in the paranasal sinuses, is prevalent in CF patients, although many are only mildly symptomatic (with few symptoms). The objective of this literature review was to discuss the pathophysiology and current therapeutic management of chronic rhinosinusitis (CRS) in CF patients. The review was based on current evidence, which was classified in accordance with the Oxford Centre for Evidence-Based Medicine criteria. When symptomatic, CRS with nasal polyps can affect quality of life and can lead to pulmonary exacerbations, given that the paranasal sinuses can be colonized with pathogenic bacteria, especially *Pseudomonas aeruginosa*. Infection with *P. aeruginosa* plays a crucial role in morbidity and mortality after lung transplantation in CF patients. Although clinical treatment of the upper airways is recommended as initial management, this recommendation is often extrapolated from studies of CRS in the general population. When sinonasal disease is refractory to noninvasive therapy, surgery is indicated. Further studies are needed in order to gain a better understanding of upper airway involvement and improve the management of CRS in CF patients, with the objective of preserving lung function and avoiding unnecessary invasive procedures.

Keywords: Nose diseases; Cystic fibrosis; Nasal polyps; Paranasal sinuses; Sinusitis.

Resumo

A fibrose cística (FC) é uma doença genética irreversível, mas os avanços no tratamento têm aumentado a expectativa de vida dos pacientes. O acometimento das vias aéreas superiores, principalmente por alterações patológicas dos seios paranasais, é prevalente nesses pacientes, embora muitos apresentem poucos sintomas. O objetivo desta revisão é discutir a fisiopatologia e o manejo terapêutico atual da rinossinusite crônica (RSC) na FC. A revisão fundamentou-se nas evidências mais recentes, classificadas em conformidade com os critérios do *Oxford Centre for Evidence-Based Medicine*. Quando sintomática, a RSC com pólipos nasais pode afetar a qualidade de vida e as exacerbações pulmonares, já que os seios paranasais podem ser colonizados por bactérias patogênicas, principalmente a *Pseudomonas aeruginosa*. Essa bactéria tem papel crucial na morbidade e mortalidade após o transplante pulmonar em pacientes com FC. Embora o tratamento clínico das vias aéreas superiores seja indicado no manejo inicial, a indicação é muitas vezes extrapolada de estudos sobre RSC na população geral. A cirurgia é a alternativa quando o quadro nasossinusal é refratário à terapia não invasiva. Mais estudos são necessários para compreender melhor o acometimento das vias aéreas superiores e melhorar o manejo da RSC na FC, a fim de preservar a função pulmonar e evitar procedimentos invasivos desnecessários.

Descritores: Doenças nasais; Fibrose cística; Pólipos nasais; Seios paranasais; Sinusite.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease that is irreversible. It has been mapped on the long arm of chromosome 7 (7q31), which encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Approximately 1,000 CF-causing mutations

have been identified, the most common being $\Delta F508$.[1] In general, CF presents as multisystem impairment, characterized by progressive lung disease, exocrine pancreatic insufficiency, liver disease, intestinal motility disorder, male infertility, and high concentrations of sweat electrolytes as a result of mucus hyperviscosity.[2]

It is well established that CF patients have upper airway involvement, and many develop chronic rhinosinusitis (CRS), which has a negative effect on their quality of life. Advances in treatment have increased the life expectancy of CF patients in recent years.[3] This increase in life expectancy has increased the focus on the management of comorbidities, including sinonasal disease. The objective of the present review was to discuss the pathophysiology, symptoms, diagnosis, and therapeutic management of sinonasal disease in CF patients, as well as the influence of CRS on lung disease in such patients.

Methods

We searched the MEDLINE (PubMed), SciELO, and Cochrane Library databases using the search terms and Boolean operators (cystic fibrosis [Title]) AND (sinusites [Title/Abstract] OR paranasal sinuses [Title/Abstract] OR upper airways [Title/Abstract]) in order to identify titles and abstracts of original and review articles published between 1960 and 2013. The search was limited to articles in English, Spanish, or Portuguese. We selected the most recent and relevant articles in order to provide an update on the treatment of sinonasal disease in CF patients.

Criteria for the diagnosis of CRS and nasal polyposis

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012,[4] rhinosinusitis in adults is defined as inflammation of the nose and paranasal sinuses with two or more of the following symptoms:
- nasal congestion
- anterior or posterior nasal drip
- facial pain or pressure
- reduction or loss of smell

These symptoms can be accompanied by endoscopic signs (of nasal polyps, mucopurulent discharge primarily from the middle meatus, edema/mucosal obstruction primarily in the middle meatus, or any combination of the three),

radiographic changes in the paranasal sinuses, or both. On the basis of its duration, the disease can be classified as acute/intermittent (< 12 weeks with complete resolution of symptoms) or chronic/persistent (≥ 12 weeks without complete resolution of symptoms).

Nasal polyposis is considered to be a subgroup of CRS.[4] In patients with CF, the finding of extensive radiographic changes in the absence of symptoms or endoscopic signs is common, its true clinical significance being unclear.[5]

Epidemiology

Although CF has a varied phenotypic presentation, pulmonary and sinonasal involvement occurs in 90-100% of CF patients.[6] Approximately 80% of patients with CF have nasal obstruction, 25% have anosmia, and more than 50% complain of rhinorrhea and headache.[7] The prevalence of nasal polyposis in patients with CF appears to depend on age, increasing during adolescence and ranging from 6% to 48%.[8]

Pathogenesis of sinonasal disease in CF patients

Although ciliary structure and beat frequency are normal in CF patients, many factors appear to contribute to impaired mucociliary clearance in such patients. First, changes in the viscoelastic properties of mucus, which are secondary to abnormal chloride conductance, appear to have a crucial role in the development of sinonasal disease. Colonization with *Pseudomonas aeruginosa*, which has a high affinity for the respiratory mucosa, also appears to contribute to impaired clearance. The presence of bacteria releases many substances, including homolysine and phenazine derivatives. They reduce ciliary beat frequency, and chronic inflammation causes goblet cell hyperplasia, squamous metaplasia, and hair cell loss. Macroscopically, these factors lead to sinus ostial obstruction, resulting in infected mucus stasis, local inflammation, and impaired gas exchange. Increased $PaCO_2$ causes mucosal edema, decreased ciliary function, and, consequently, bacterial colonization.[1]

It has been suggested that there is a relationship between the genotype-phenotype correlation and CRS. A high risk of nasal polyposis has been found in patients homozygous for $\Delta F508$ or

other severe mutations (Figure 1), although with no clear correlation with the severity of CF.[9] This hypothesis was not confirmed, and some studies even showed improved lung function and nutritional status in CF patients with nasal polyposis.[10,11] Genetic studies have suggested that the CFTR mutation responsible for CF is in itself a predisposing factor for sinonasal disease, showing an increased prevalence of CFTR mutations in the general population with CRS.[12]

Sinonasal anatomic changes are common in patients with CF. Several factors contribute to sinus hypoplasia, including growth disorders secondary to severe chronic infections and early inflammation or changes in growth and embryogenesis caused by a genetic mutation. Erosion of the lateral nasal wall is assumed to be due to osteitis or the pressure exerted by polyps or thick mucus on the medial wall of the sinus, leading to the formation of "pseudomucocele" (Figure 2).[13] In pediatric patients, the aforementioned changes should raise the suspicion of CF.[14] One study showed that patients homozygous for ΔF508 were more likely to have frontal, maxillary, and sphenoid sinus hypoplasia than were those with other mutations in the CFTR protein.[14]

The reason why the prevalence of nasal polyposis is high remains unclear, as does the pathophysiology of the disease. Possible explanations include atopy and nasal obstruction causing impaired blood circulation.[15] Studies conducted in the 1990s showed that the prevalence of atopy was no higher in CF patients than in the general population.[16] In addition, the histopathology of CF differs from that of atopy-related polyps by the absence of eosinophilic infiltrate. It is of note that a unique etiology for nasal polyposis does not explain the pathogenesis of the disease, chronic inflammation probably being the most relevant factor.[5]

Role of the upper airways in lung disease

In patients with CF, sinonasal involvement can exacerbate lung disease, the upper airways serving as a bacterial reservoir. Postnasal drip has been considered a major cause of lower respiratory tract infections, possibly because the bacterial florae in the paranasal sinuses and lower airways are identical.[17]

Sinus obstruction secondary to thick, impacted mucus contributes to the presence of microorganisms throughout the respiratory tree. Failure of the upper airways to filter, humidify, and warm inhaled air can be an aggravating factor in the deterioration of lung function as a result of repeated infections. This allows chronic colonization of the airways with pathogens such as *Pseudomonas* spp., which compromise airway immunity.[18]
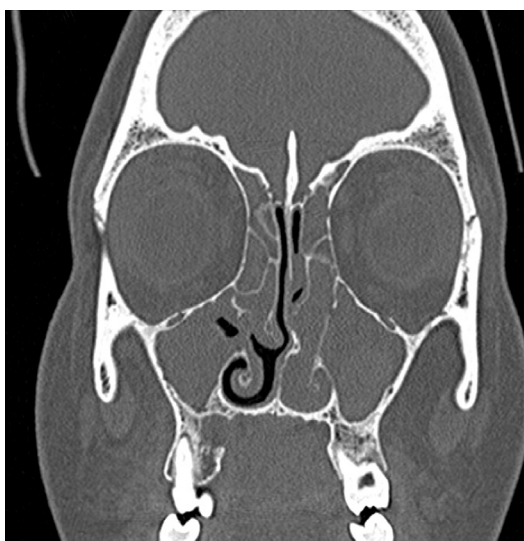
Figure 1 – Nasal polyposis in a ΔF508 homozygous adolescent with cystic fibrosis.
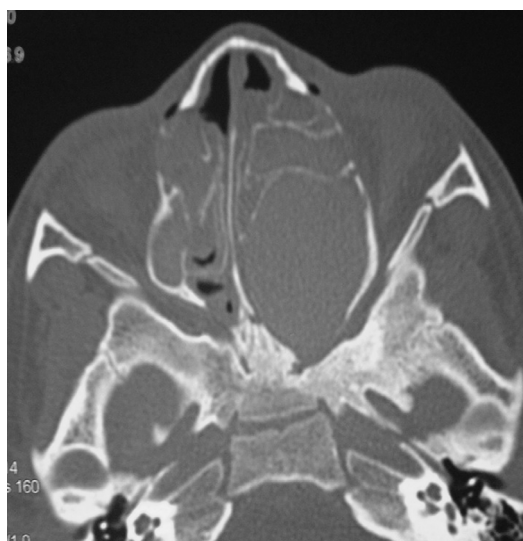
Figure 2 – Ethmoid sinus pseudomucocele in a 6-year-old child with cystic fibrosis.

Sinonasal disease and lung transplantation

In lung transplant recipients, the major cause of morbidity and mortality is *P. aeruginosa* pneumonia, which is probably a consequence of sinonasal colonization. One study showed a significant correlation between bacterial colonization of the paranasal sinuses and lung graft infection (primarily with *P. aeruginosa*) after functional endoscopic sinus surgery (FESS). Patients who had undergone FESS before lung transplantation were found to have lower paranasal bacterial counts, which were correlated with reduced bacterial cultures in bronchoalveolar lavage fluid.[19] An early study showed that daily catheter instillation of tobramycin via maxillary sinus antrostomy resulted in negative cultures for *P. aeruginosa*.[20] Another comparative study, similar to the aforementioned study, showed reduced recurrence of CRS after FESS and nasal lavage with tobramycin, although no significant differences were found regarding colonization with *P. aeruginosa*.[17]

Diagnosis

History taking and physical examination

The symptoms of rhinosinusitis are underreported; only 10% of pediatric and adolescent patients with CF have significant complaints of sinonasal symptoms, despite changes in imaging and endoscopic findings.[7] This adaptation to sinonasal symptoms is due to the absence of a healthy baseline for comparison. When symptoms occur, nasal polyposis (Figure 3) with consequent nasal obstruction is the main complaint. In addition, as can be seen in Figure 4, bulging of the lateral nasal wall can exacerbate the obstruction.[8]

In a retrospective study of pediatric patients, initial symptoms included nasal obstruction (in 62%), rhinorrhea (in 64%), and mouth breathing (in 38%). Chronic complaints included cough (in 60%), sleep disturbances (in 37%), headache (in 32%), and anosmia (in 12%).[7] Headache is more prevalent in adolescents and adults, often becoming a chronic symptom.[3]

Physical examination can provide evidence of sinonasal disease, including facial deformity, broadening of the nasal root, hypertelorism, and proptosis. Anterior rhinoscopy and endoscopic examination can reveal congestion and hyperemia of the nasal mucosa, abundant secretion, polyps, and medial bulging of the lateral nasal wall.[7]

Imaging

Imaging of the paranasal sinuses of CF patients reveals specific features, such as frontal and sphenoid sinus hypoplasia (Figure
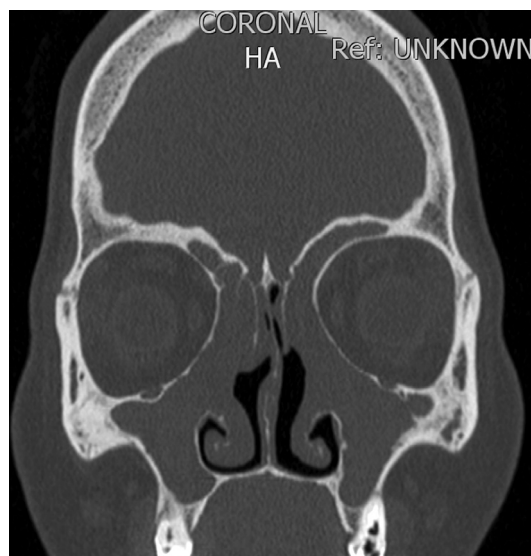
Figure 3 – Widespread nasal polyposis and frontal sinus hypoplasia in an adult cystic fibrosis patient who had undergone nasal surgery and had no sinonasal symptoms.
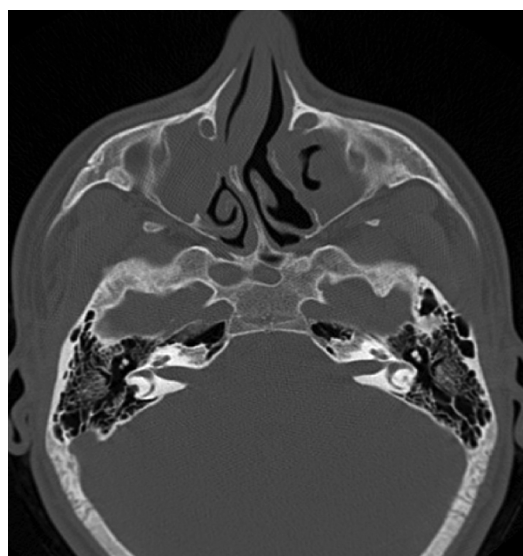
Figure 4 – Medial bulging of the lateral nasal wall with obstructive septal deviation in an adult patient with cystic fibrosis, causing symptoms of bilateral nasal obstruction.

5), demineralization of the uncinate process, and medial bulging of the lateral nasal wall.[21] In most CF patients, CT imaging shows opacified paranasal sinuses after the age of 8 months. There are fewer sinus pneumatization variants, such as Haller cells and agger nasi cells. The maxillary sinuses are usually reduced in size, and the posterior ethmoid sinus usually grows faster than does the anterior ethmoid sinus, causing an inversion of their relationship throughout the ethmoid labyrinth.[7] The presence of frontal sinus agenesis (Figure 6) and maxilloethmoid sinus opacification greater than 75% have been proposed as pathognomonic criteria for CF.[22]

CT is the gold standard imaging modality, especially for surgical planning. However, CT findings are not useful as an outcome measure for clinical or surgical interventions for CRS.[23] Although nuclear magnetic resonance imaging allows better differentiation among mucosa, polyps, and retained secretions than does CT, it does not clearly show bony structures.[24]

Bacteriology of the paranasal sinuses

Sputum examination and middle meatus aspiration culture are used in order to guide antibiotic therapy. The most prevalent pathogens in CF patients are *Staphylococcus aureus* and *P.*

aeruginosa, the latter being the most responsible for the destruction of lung parenchyma. Pulmonary colonization with *P. aeruginosa* has been significantly correlated with the presence of nasal polyposis, the prevalence of which has been reported to increase with the duration of colonization with the pathogen.[25] The phenotypic change by *P. aeruginosa* (to mucoid growth in macrocolonies, which inhibit phagocytosis) is the main factor for persistent airway infection, *P. aeruginosa* forming a biofilm and increasing its resistance, despite an intense inflammatory response.[26] Early identification of *Pseudomonas* spp. infection is essential for the initiation of eradication therapy, the objective of which is to prevent or delay chronic infection with the bacteria at a phase in which strains are more susceptible to antibiotics.[27]

Other common bacteria in CF patients include *Haemophilus influenzae*, *Burkholderia cepacia*, *Achromobacter xylosoxidans*, and *Stenotrophomonas maltophilia*.[16] Despite the impaired mucociliary clearance inherent to CF, patients with the disease are no more susceptible to viral upper respiratory tract infections than are those without it.[28]

Nonbacterial pathogens such as *Aspergillus* spp. are also found in sinus aspirates from more than 40% of adults with CF, a finding that signifies colonization more than it does invasive disease.[29]

Figure 5 – Axial CT scan of the sinuses showing sphenoid sinus hypoplasia in a 25-year-old patient with cystic fibrosis.

Figure 6 – Sagittal CT scan of the sinuses showing frontal sinus aplasia in a 40-year-old patient with cystic fibrosis.

In a study specifically aimed at detecting fungal sinonasal disease in CF patients, 33.3% of the cultures were positive for fungi, *Candida albicans* being the most frequently isolated species. Other isolated fungi included *A. fumigatus*, *Bipolaris* spp., *Exserohilum* spp., and *Penicillium* spp.[30]

Clinical treatment

Conservative management is considered the first step in the treatment of CRS in CF patients. Various treatments with nasal corticosteroid sprays, decongestants, antihistamines, and saline irrigation are routinely used without a specific assessment of their efficacy. Table 1 summarizes the therapies used in CRS patients (with and without CF), the levels of evidence and grades of recommendation being based on the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[31]

Nasal lavage

Normal saline (0.9% saline solution) or hypertonic saline is used in order to wash secretions, debris, and nasal crusts. Hypertonic saline has the advantage of having an osmotic decongestant effect on the nasal mucosa; however, it causes mild, reversible ciliostasis.[32] A Cochrane meta-analysis concluded that the quality of life of patients with CRS was better with nasal lavage than without it.[33] There are no studies of CF patients with CRS, and these recommendations are extrapolated from studies of patients without CF. Although it is advocated that 7% saline solution is more appropriate for CF patients because of its mucolytic effect, resulting in improved quality of life and reduced pulmonary exacerbations,[34] the commercially available 3% saline solutions are the most widely used (level of evidence: IV; grade D recommendation).

Nasal decongestants

Nasal decongestants (oxymetazoline, phenylephrine, and xylometazoline) reduce inferior turbinate congestion but do not directly affect the maxillary and ethmoid sinuses. Rebound congestion can occur when nasal decongestants are used for more than 1 week, causing physical dependence and drug-induced rhinitis,[35] their routine use therefore being contraindicated (level of evidence: IV; grade D recommendation).

Nasal corticosteroids

We found only one randomized clinical trial (RCT) of a topical nasal corticosteroid in CF patients, who received 100 µg of betamethasone nasal drops twice a day for 6 weeks. The study showed a significant reduction in polyp size.[36] Although CF polyps have a histological predominance of neutrophils, which theoretically do not respond to steroids, studies have shown positive effects of steroid use, which are

Table 1 – Levels of evidence and grades of recommendation of studies on the treatment of chronic rhinosinusitis in patients with and without cystic fibrosis.[a]

Treatment	Patients without CF		Patients with CF
	CRSsNP	CRSwNP	CRS
0.9% saline nasal irrigation	Ia (A)	Ib (D)	IV (D)
3% saline nasal irrigation	Ia (A)	Ib (D)	IV (D)
7% hypertonic saline nebulization	N/A	N/A	N/A
Oral antibiotics < 4 weeks	II (B)	Ib/Ib(–)* (C)	ND
Oral antibiotics > 12 weeks	Ib (C)	III (C)	III (C)
Macrolides	Ib (C)	III (C)	III (C)
Topical nasal antibiotics	Ib(–)[b](A–)[c]	SDD	IIb (B)
Systemic corticosteroids	IV (C)	Ia (A)	IV (D)
Nasal corticosteroids	Ia (A)	Ia (A)	Ib (A)
Recombinant human DNase	ND	ND	IIa (B)
Nasal decongestants	ND	ND	IV (D)
Leukotriene receptor antagonists	ND	Ib(–)*	ND
Ibuprofen	ND	N/A	IV (D)
FESS alone	III	III	III (B/C)

CF: cystic fibrosis; CRSsNP: chronic rhinosinusitis without nasal polyposis; CRSwNP: chronic rhinosinusitis with nasal polyposis; ND: no data; and FESS: functional endoscopic sinus surgery. [a]In accordance with the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[31] [b]Ib(–): category Ib evidence from a study with a negative outcome. [c](A–): grade A recommendation against use.

probably due to the anti-inflammatory effect of steroids[37] (level of evidence: Ib; grade A recommendation).

Oral corticosteroids

Short-term use of oral corticosteroids in the beginning of rhinosinusitis treatment with antibiotics can improve the therapeutic effects; however, this issue remains controversial. CRS nearly always coexists with lung disease, and patients receive multiple courses of antibiotics for the treatment of pulmonary exacerbations. The frequent use of antibiotics can explain the reduced incidence of rhinosinusitis complications.[38] A Cochrane review of RCTs of oral corticosteroid use in CF patients showed slower progression of lung disease, fewer hospitalizations for respiratory exacerbations, and better quality of life but no effects on sinonasal symptoms.[39] Although oral corticosteroids are widely recommended for patients with CRS, there is surprisingly little evidence for oral corticosteroid use, especially in CRS patients without nasal polyposis (level of evidence: IV; grade D recommendation).

Recombinant human DNase

Recombinant human DNase reduces the viscosity of secretions in the airways of CF patients by cleavage of extracellular DNA. One study investigated nasal inhalation of recombinant human DNase in patients undergoing FESS, showing that there was a reduction in mucosal edema more than 3 years after surgery, lower recurrence of nasal polyps, and less need for sinonasal procedures in the treatment group.[40] One RCT showed that treatment with recombinant human DNase for 8 weeks improved nasal symptoms, as well as the CT and endoscopic appearance of the paranasal sinuses. However, the efficacy of recombinant human DNase appears to depend on surgical enlargement of the paranasal sinus ostia to allow the drug to be delivered to the sinus mucosa[35] (level of evidence: IIa; grade B recommendation).

Oral antibiotics

Antibiotics constitute an integral component of the pharmacological management of rhinosinusitis in CF patients and are generally used for a period of 3-6 weeks.[16] Although the ideal duration of treatment has yet to be defined, long-course antibiotic therapy is recommended for CF patients because of mucociliary function changes caused by abnormal ion transport and the presence of bacterial agents (*P. aeruginosa* and *Streptococcus pneumoniae*) inducing a greater reduction in mucociliary clearance.[41]

Although the choice of antibiotic therapy is empirical, the selected treatment should provide coverage for *P. aeruginosa*, which is one of the most common pathogens found in the lower and upper airways of CF patients. Drugs such as ciprofloxacin and azithromycin are the most widely used for prophylaxis and exacerbation control.[6]

Long-term use of azithromycin reduces airway inflammation and lung parenchymal destruction in patients colonized with *P. aeruginosa*, a finding that has been confirmed in RCTs.[42,43] Possible mechanisms of action include direct effects on the pathogen and the host. A decrease in bacterial virulence, especially in *P. aeruginosa* virulence, and a late bactericidal effect, as well as a decrease in airway adherence of, motility of, and biofilm production by *Pseudomonas* spp., are the potential effects of the agent.[44]

Low doses of macrolides for prolonged periods have been used in CRS patients because macrolides play a role in modulating chronic inflammation. Macrolides are promising in the treatment of CRS because of their additional effect of reducing IL-8 production and, consequently, the size of nasal polyps (level of evidence: III; grade C recommendation).[45]

Topical antibiotics

Tobramycin belongs to the aminoglycoside class of antibiotics, and the use of inhaled tobramycin in the treatment of chronic lower airway infections with *P. aeruginosa* is well established.[41] One systematic review showed that there was insufficient evidence for the widespread use of tobramycin in patients with CRS, although tobramycin was reported to be significantly beneficial in patients with CF and CRS, especially in the postoperative management of patients undergoing FESS.[46] Although the use of inhaled colistin and aztreonam in the treatment of the lower airways is based on strong evidence, there are no studies on the use of inhaled colistin and aztreonam in the treatment of CRS in CF patients (level of evidence: IIb; grade B recommendation).[5]

Leukotriene receptor antagonists

Leukotrienes are inflammatory mediators found in various diseases of the respiratory tract. Patients with rhinitis and severe corticosteroid-dependent asthma with salicylate intolerance can be safely treated with leukotriene receptor antagonists (montelukast and zafirlukast). Because of their anti-inflammatory activity, leukotriene receptor antagonists are recommended for patients with CRS with nasal polyposis as an alternative to oral corticosteroids, being used in combination with topical corticosteroids. A recent meta-analysis showed a small improvement in sinonasal symptoms in patients with CRS and nasal polyposis without CF; however, the results obtained with the use of leukotriene receptor antagonists in combination with nasal corticosteroids were of no clinical relevance.[47] One RCT showed that montelukast reduces eosinophilic inflammation in CF patients and has positive effects on lung function, suggesting a beneficial role in preventing remodeling and bronchiolar disease.[48] There are currently no data regarding leukotriene receptor antagonists and CRS in CF patients (no evidence available).

Surgical treatment

Many CF patients do not respond satisfactorily to the clinical management of CRS, 10-20% undergoing paranasal sinus surgery. Many eventually require revision surgery because of chronic sinus disease.[49] The indication of routine FEES for the treatment of sinonasal disease in CF patients is controversial, given that the severity of its clinical presentation is subject to multifactorial influences. Patients who benefit most from surgery are those who develop recurrent disease as a result of an anatomic abnormality that obstructs sinus drainage, particularly in the presence of nasal polyposis.[42] Several patients present with complete opacification of the maxillary sinus and normal aeration of the ethmoid sinuses. In such patients, advanced disease limited to the maxillary sinus (similar to mucoceles) might cause few symptoms, requiring no surgical treatment.[5]

Because of the chronic nature of the disease and because the primary objective of surgical treatment is symptom improvement, less invasive procedures, such as polypectomy, have been proposed. However, studies have shown that early recurrence of nasal polyps is more likely in patients undergoing polypectomy alone than in those undergoing polypectomy and procedures that are more extensive, such as intranasal ethmoidectomy and antrostomy.[50,51] It has been reported that FESS should be performed in CF patients with persistent nasal obstruction after clinical treatment; in those with endoscopic or CT findings of anatomic obstruction; in those in whom there is a correlation between sinonasal symptoms and pulmonary exacerbations, especially before lung transplantation; and in those in whom symptoms such as facial pain and headache affect quality of life.[22]

One study showed a reduction in hospitalizations in CF patients in the first 6 months after FESS.[52] A recent systematic review showed that FESS is safe in patients with CF, and that there is improvement in subjective symptoms, such as nasal obstruction, rhinorrhea, headache, facial pain, and anosmia. However, the authors found no improvement in pulmonary function test results after surgery.[53] After that systematic review, a prospective cohort study examined the effects of FESS with adjuvant antibiotic therapy on bacterial colonization of the lower airways 1 year after surgery. The results of the study showed significantly decreased growth of pathogenic bacteria in sputum cultures after FESS, particularly in CF patients in whom sinonasal and sputum cultures were positive for the same pathogen (level of evidence: III; grade B/C recommendation).[54]

Future research

Intranasal gentamicin

Topical application of gentamicin appears to reduce nasal potential difference in CF patients as a result of the mechanism of correction of *CFTR* allele expression. Nasal aminoglycosides delivered via nebulization have been studied in CRS patients without CF and have been found to decrease nasal bacterial colonization and the inflammatory response.[55]

Ibuprofen

Recent studies have described the therapeutic effects of high doses of ibuprofen in the treatment of progressive lung disease in children with CF. Although ibuprofen was found to be beneficial in a small case series of patients with CF and

nasal polyposis, larger studies are needed in order to evaluate its efficacy.[56]

CFTR modulators

New therapeutic strategies aimed at rescuing CFTR activity have been approved for selected groups of CF patients. Drugs that have undergone clinical testing include ivacaftor (VX-770), lumacaftor (VX-809), and ataluren (PTC124). Ivacaftor resulted in significant improvement in lung function in CF patients with the G551D mutation and was recently approved by the U.S. Food and Drug Administration for use in individuals who are over 6 years of age and have specific mutations.[57] To date, there have been no studies examining the effects of CFTR modulators on the sinonasal mucosa. However, given that these new molecules attempt to "potentiate" defective chloride channels, they are assumed to have a beneficial effect on sinonasal disease in certain CF patients.

Gene therapy

Although gene therapy is considered the ultimate solution for CF, it is still under study. There have been gene transfer studies targeting the nasal cavities.[58] One RCT studied the *CFTR* gene, which was transferred to the nasal mucosa via an adeno-associated virus. The method rectified abnormal nasal potential difference measurements and reduced the recurrence of rhinosinusitis during the first month.[59]

Balloon catheter sinuplasty

Balloon catheter sinuplasty is a new therapeutic alternative for patients with CRS. It was introduced in 2006 and has been shown to be as effective as FESS. It has recently been evaluated for the treatment of CRS in pediatric patients. Balloon catheter sinuplasty has proven safe and effective and has the advantage of not involving tissue removal, sparing the mucosa.[60] Although there have been no studies of balloon catheter sinuplasty in patients with CF, the procedure is a less invasive alternative for the treatment of CRS patients, particularly pediatric patients.

Final considerations

Sinonasal disease is common in children and adults with CF. In patients with CRS, the findings of noneosinophilic nasal polyps and unusual bacteria or specific radiographic findings are suggestive of CF, even in the absence of gastrointestinal or pulmonary symptoms. Children with CRS should be considered CF patients until proven otherwise and should always be screened for the disease. When symptomatic, CRS with nasal polyposis impairs the filtering function of the upper airways, contributing to the colonization of the nasal sinuses with pathogens such as *P. aeruginosa*.

The pathophysiology of CF predisposes the sinonasal mucosa to chronic inflammation and recurrent infections caused by mucus stasis and anatomic changes that decrease sinus aeration. The severity of sinonasal disease can affect pulmonary status and contribute to pulmonary exacerbations. When conservative treatment does not resolve the symptoms and when sinonasal disease is related to deterioration of lung disease, FESS plays an important role. However, the diseased mucosa remains after surgery, leading to high rates of recurrence of CRS. Further studies on perioperative management are therefore required, focusing on the use of preoperative and postoperative antibiotics and anti-inflammatory agents. Such studies can help to improve the management of CRS, thus preventing recurrence and avoiding revision procedures.

References

1. Tandon R, Derkay C. Contemporary management of rhinosinusitis and cystic fibrosis. Curr Opin Otolaryngol Head Neck Surg. 2003;11(1):41-4. http://dx.doi.org/10.1097/00020840-200302000-00009
2. Dalcin Pde T, Abreu E Silva FA. Cystic fibrosis in adults: diagnostic and therapeutic aspects. J Bras Pneumol. 2008;34(2):107-17.
3. Mak GK, Henig NR. Sinus disease in cystic fibrosis. Clin Rev Allergy Immunol. 2001;21(1):51-63. http://dx.doi.org/10.1385/CRIAI:21:1:51
4. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl. 2012;(23):3 p preceding table of contents, 1-298.
5. Mainz JG, Koitschev A. Pathogenesis and management of nasal polyposis in cystic fibrosis. Curr Allergy Asthma Rep. 2012;12(2):163-74. http://dx.doi.org/10.1007/s11882-012-0250-y
6. Oomen KP, April MM. Sinonasal manifestations in cystic fibrosis. Int J Otolaryngol. 2012;2012:789572.
7. Brihaye P, Jorissen M, Clement PA. Chronic rhinosinusitis in cystic fibrosis (mucoviscidosis). Acta Otorhinolaryngol Belg. 1997;51(4):323-37.
8. Steinke JW, Payne SC, Chen PG, Negri J, Stelow EB, Borish L. Etiology of nasal polyps in cystic fibrosis: not a unimodal

disease. Ann Otol Rhinol Laryngol. 2012;121(9):579-86. http://dx.doi.org/10.1177/000348941212100904

9. Feuillet-Fieux MN, Lenoir G, Sermet I, Elie C, Djadi-Prat J, Ferrec M, et al. Nasal polyposis and cystic fibrosis(CF): review of the literature. Rhinology. 2011;49(3):347-55.

10. Marshak T, Rivlin Y, Bentur L, Ronen O, Uri N. Prevalence of rhinosinusitis among atypical cystic fibrosis patients. Eur Arch Otorhinolaryngol. 2011;268(4):519-24. http://dx.doi.org/10.1007/s00405-010-1382-0

11. Cimmino M, Cavaliere M, Nardone M, Plantulli A, Orefice A, Esposito V, et al. Clinical characteristics and genotype analysis of patients with cystic fibrosis and nasal polyposis. Clin Otolaryngol Allied Sci. 2003;28(2):125-32. http://dx.doi.org/10.1046/j.1365-2273.2003.00677.x

12. Wang X, Moylan B, Leopold DA, Kim J, Rubenstein RC, Togias A et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. JAMA. 2000;284(14):1814-9. http://dx.doi.org/10.1001/jama.284.14.1814

13. Woodworth BA, Ahn C, Flume PA, Schlosser RJ. The delta F508 mutation in cystic fibrosis and impact on sinus development. Am J Rhinol. 2007;21(1):122-7. http://dx.doi.org/10.2500/ajr.2007.21.2905

14. April MM, Tunkel DE, DeCelie-Germana J, Zeitlin PL, Zinreich SJ. Computed Tomography (CT) Scan Findings of the Paranasal Sinuses in Cystic Fibrosis. Am J Rhinol. 1995;9(5):277-80. http://dx.doi.org/10.2500/105065895781808892

15. Tos M, Mogensen C, Thomsen J. Nasal polyps in cystic fibrosis. J Laryngol Otol. 1977;91(10):827-35. http://dx.doi.org/10.1017/S0022215100084449

16. Ramsey B, Richardson MA. Impact of sinusitis in cystic fibrosis. J Allergy Clin Immunol. 1992;90(3 Pt 2):547-52. http://dx.doi.org/10.1016/0091-6749(92)90183-3

17. Moss RB, King VV. Management of sinusitis in cystic fibrosis by endoscopic surgery and serial antimicrobial lavage. Reduction in recurrence requiring surgery. Arch Otolaryngol Head Neck Surg. 1995;121(5):566-72. http://dx.doi.org/10.1001/archotol.1995.01890050058011

18. Davidson TM, Murphy C, Mitchell M, Smith C, Light M. Management of chronic sinusitis in cystic fibrosis. Laryngoscope. 1995;105(4 Pt 1):354-8. http://dx.doi.org/10.1288/00005537-199504000-00002

19. Nunley DR, Grgurich W, Iacono AT, Yousem S, Ohori NP, Keenan RJ, et al. Allograft colonization and infections with pseudomonas in cystic fibrosis lung transplant recipients. Chest. 1998;113(5):1235-43. http://dx.doi.org/10.1378/chest.113.5.1235

20. Lewiston N, King V, Umetsu D, Starnes V, Marshall S, Kramer M, et al. Cystic fibrosis patients who have undergone heart-lung transplantation benefit from maxillary sinus antrostomy and repeated sinus lavage. Transplant Proc. 1991;23(1 Pt 2):1207-8.

21. Eggesbø HB, Søvik S, Dølvik S, Kolmannskog F. CT characterization of inflammatory paranasal sinus disease in cystic fibrosis. Acta Radiol. 2002;43(1):21-8. http://dx.doi.org/10.1080/028418502127347592

22. Nishioka GJ, Cook PR, McKinsey JP, Rodriguez FJ. Paranasal sinus computed tomography scan findings in patients with cystic fibrosis. Otolaryngol Head Neck Surg. 1996;114(3):394-9. http://dx.doi.org/10.1016/S0194-5998(96)70208-5

23. McMurphy AB, Morriss C, Roberts DB, Friedman EM. The usefulness of computed tomography scans in cystic fibrosis patients with chronic sinusitis. Am J Rhinol. 2007;21(6):706-10. http://dx.doi.org/10.2500/ajr.2007.21.3104

24. Graham SM, Launspach JL, Welsh MJ, Zabner J. Sequential magnetic resonance imaging analysis of the maxillary sinuses: implications for a model of gene therapy in cystic fibrosis. J Laryngol Otol. 1999;113(4):329-35.

25. Henriksson G, Westrin KM, Karpati F, Wikström AC, Stierna P, Hjelte L. Nasal polyps in cystic fibrosis: clinical endoscopic study with nasal lavage fluid analysis. Chest. 2002;121(1):40-7. http://dx.doi.org/10.1378/chest.121.1.40

26. Johansen HK, Aanaes K, Pressler T, Nielsen KG, Fisker J, Skov M, et al. Colonisation and infection of the paranasal sinuses in cystic fibrosis patients is accompanied by a reduced PMN response. J Cyst Fibros. 2012;11(6):525-31. http://dx.doi.org/10.1016/j.jcf.2012.04.011

27. Silva Filho LV, Ferreira Fde A, Reis FJ, Britto MC, Levy CE, Clark O, et al. Pseudomonas aeruginosa infection in patients with cystic fibrosis: scientific evidence regarding clinical impact, diagnosis, and treatment. J Bras Pneumol. 2013;39(4):495-512. http://dx.doi.org/10.1590/S1806-37132013000400015

28. Ramsey BW, Gore EJ, Smith AL, Cooney MK, Redding GJ, Foy H. The effect of respiratory viral infections on patients with cystic fibrosis. Am J Dis Child. 1989;143(6):662-8.

29. Bargon J, Dauletbaev N, Köhler B, Wolf M, Posselt HG, Wagner TO. Prophylactic antibiotic therapy is associated with an increased prevalence of Aspergillus colonization in adult cystic fibrosis patients. Respir Med. 1999;93(11):835-8. http://dx.doi.org/10.1016/S0954-6111(99)90270-6

30. Muhlebach MS, Miller MB, Moore C, Wedd JP, Drake AF, Leigh MW. Are lower airway or throat cultures predictive of sinus bacteriology in cystic fibrosis? Pediatr Pulmonol. 2006;41(5):445-51. http://dx.doi.org/10.1002/ppul.20396

31. Centre For Evidence-Based Medicine (CEBM) [homepage on the Internet]. Oxford: CEBM [cited 2014 Jun 23]. The Oxford 2011 Levels of Evidence. Available from: http://www.cebm.net/index.aspx?o=5653

32. Boek WM, Keles N, Graamans K, Huizing EH. Physiologic and hypertonic saline solutions impair ciliary activity in vitro. Laryngoscope. 1999;109(3):396-9. http://dx.doi.org/10.1097/00005537-199903000-00010

33. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev. 2007;(3):CD006394.

34. Elkins MR, Bye PT. Inhaled hypertonic saline as a therapy for cystic fibrosis. Curr Opin Pulm Med. 2006;12(6):445-52. http://dx.doi.org/10.1097/01.mcp.0000245714.89632.b2

35. Mainz JG, Koitschev A. Management of chronic rhinosinusitis in CF. J Cyst Fibros. 2009;8 Suppl 1:S10-4. http://dx.doi.org/10.1016/S1569-1993(09)60005-9

36. Hadfield PJ, Rowe-Jones JM, Mackay IS. A prospective treatment trial of nasal polyps in adults with cystic fibrosis. Rhinology. 2000;38(2):63-5.

37. Costantini D, Di Cicco M, Giunta A, Amabile G. Nasal polyposis in cystic fibrosis treated by beclomethasone dipropionate. Acta Univ Carol Med (Praha). 1990;36(1-4):220-1.

38. Jaffe BF, Strome M, Khaw KT, Shwachman H. Nasal polypectomy and sinus surgery for cystic fibrosis--a 10 year review. Otolaryngol Clin North Am. 1977;10(1):81-90.

39. Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. Cochrane Database Syst Rev. 2013;6:CD000407.

40. Raynor EM, Butler A, Guill M, Bent JP 3rd. Nasally inhaled dornase alfa in the postoperative management of chronic sinusitis due to cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2000;126(5):581-3. http://dx.doi.org/10.1001/archotol.126.5.581

41. Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis, and management. Pediatr Pulmonol. 2000;30(6):481-9. http://dx.doi.org/10.1002/1099-0496(200012)30:6<481::AID-PPUL8>3.0.CO;2-N

42. Jaffé A, Francis J, Rosenthal M, Bush A. Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet. 1998;351(9100):420. http://dx.doi.org/10.1016/S0140-6736(05)78360-4

43. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2003;290(13):1749-56. http://dx.doi.org/10.1001/jama.290.13.1749

44. Luisi F, Gandolfi TD, Daudt AD, Sanvitto JP, Pitrez PM, Pinto LA. Anti-inflammatory effects of macrolides in childhood lung diseases. J Bras Pneumol. 2012;38(6):786-96. http://dx.doi.org/10.1590/S1806-37132012000600016

45. Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. Am J Rhinol. 2000;14(3):143-8. http://dx.doi.org/10.2500/105065800782102717

46. Lim M, Citardi MJ, Leong JL. Topical antimicrobials in the management of chronic rhinosinusitis: a systematic review. Am J Rhinol. 2008;22(4):381-9. http://dx.doi.org/10.2500/ajr.2008.22.3189

47. Wentzel JL, Soler ZM, DeYoung K, Nguyen SA, Lohia S, Schlosser RJ. Leukotriene antagonists in nasal polyposis: a meta-analysis and systematic review. Am J Rhinol Allergy. 2013;27(6):482-9. http://dx.doi.org/10.2500/ajra.2013.27.3976

48. Schmitt-Grohé S, Eickmeier O, Schubert R, Bez C, Zielen S. Anti-inflammatory effects of montelukast in mild cystic fibrosis. Ann Allergy Asthma Immunol. 2002;89(6):599-605. http://dx.doi.org/10.1016/S1081-1206(10)62108-4

49. Robertson JM, Friedman EM, Rubin BK. Nasal and sinus disease in cystic fibrosis. Paediatr Respir Rev. 2008;9(3):213-9. http://dx.doi.org/10.1016/j.prrv.2008.04.003

50. Crockett DM, McGill TJ, Healy GB, Friedman EM, Salkeld LJ. Nasal and paranasal sinus surgery in children with cystic fibrosis. Ann Otol Rhinol Laryngol. 1987;96(4):367-72. http://dx.doi.org/10.1177/000348948709600403

51. Cepero R, Smith RJ, Catlin FI, Bressler KL, Furuta GT, Shandera KC. Cystic fibrosis--an otolaryngologic perspective. Otolaryngol Head Neck Surg. 1987;97(4):356-60.

52. Rosbe KW, Jones DT, Rahbar R, Lahiri T, Auerbach AD. Endoscopic sinus surgery in cystic fibrosis: do patients benefit from surgery? Int J Pediatr Otorhinolaryngol. 2001;61(2):113-9. http://dx.doi.org/10.1016/S0165-5876(01)00556-0

53. Macdonald KI, Gipsman A, Magit A, Fandino M, Massoud E, Witterick IJ, et al. Endoscopic sinus surgery in patients with cystic fibrosis: a systematic review and meta-analysis of pulmonary function. Rhinology. 2012;50(4):360-9.

54. Aanaes K, Johansen HK, Skov M, Buchvald FF, Hjuler T, Pressler T, et al. Clinical effects of sinus surgery and adjuvant therapy in cystic fibrosis patients - can chronic lung infections be postponed? Rhinology. 2013;51(3):222-30.

55. Kobayashi T, Baba S. Topical use of antibiotics for paranasal sinusitis. Rhinol Suppl. 1992;14:77-81.

56. Lindstrom DR, Conley SF, Splaingard ML, Gershan WM. Ibuprofen therapy and nasal polyposis in cystic fibrosis patients. J Otolaryngol. 2007;36(5):309-14. http://dx.doi.org/10.2310/7070.2007.0049

57. Chaaban MR, Kejner A, Rowe SM, Woodworth BA. Cystic fibrosis chronic rhinosinusitis: a comprehensive review. Am J Rhinol Allergy. 2013;27(5):387-95. http://dx.doi.org/10.2500/ajra.2013.27.3919

58. Graham SM, Launspach JL. Utility of the nasal model in gene transfer studies in cystic fibrosis. Rhinology. 1997;35(4):149-53.

59. Wagner JA, Nepomuceno IB, Shah N, Messner AH, Moran ML, Norbash AM, et al. Maxillary sinusitis as a surrogate model for CF gene therapy clinical trials in patients with antrostomies. J Gene Med. 1999;1(1):13-21. http://dx.doi.org/10.1002/(SICI)1521-2254(199901/02)1:1<13::AID-JGM6>3.3.CO;2-7

60. Sedaghat AR, Cunningham MJ. Does balloon catheter sinuplasty have a role in the surgical management of pediatric sinus disease? Laryngoscope. 2011;121(10):2053-4. http://dx.doi.org/10.1002/lary.21929

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Risk factors associated with adverse reactions to antituberculosis drugs*

Fatores de risco associados às reações adversas a medicamentos antituberculose

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Abstract

This review sought to identify the available scientific evidence on risk factors associated with adverse reactions to antituberculosis drugs. We performed a systematic review of studies published in the 1965-2012 period and indexed in the MEDLINE and LILACS databases. A total of 1,389 articles were initially selected. After reading their abstracts, we selected 85 studies. Of those 85 studies, 16 were included in the review. Risk factors for adverse reactions to antituberculosis drugs included age > 60 years, treatment regimens, alcoholism, anemia, and HIV co-infection, as well as sodium, iron, and albumin deficiency. Protective factors against hepatic adverse effects of antituberculosis drugs included being male (combined OR = 0.38; 95% CI: 0.20-0.72) and showing a rapid/intermediate N-acetyltransferase 2 acetylator phenotype (combined OR = 0.41; 95% CI: 0.18-0.90). There is evidence to support the need for management of adverse reactions to antituberculosis drugs at public health care facilities.

Keywords: Tuberculosis; Drug-related side effects and adverse reactions; Antitubercular agents; Review.

Resumo

Esta revisão buscou identificar a evidência científica disponível sobre os fatores de risco associados às reações adversas a medicamentos (RAM) antituberculose. Foi realizada uma revisão sistemática de estudos publicados entre 1965 a 2012 e indexados nas bases de dados MEDLINE e LILACS. Foram inicialmente selecionados 1.389 artigos. Após a leitura dos resumos, foram selecionados 85 estudos. Dos 85 estudos, 16 foram incluídos na revisão. Os fatores de risco de RAM foram idade > 60 anos, esquemas de tratamento, alcoolismo, anemia, coinfecção pelo HIV e deficiência de sódio, ferro e albumina. Os fatores de proteção contra RAM hepáticas foram o sexo masculino (OR combinada = 0,38; IC95%: 0,20-0,72) e o fenótipo acetilador rápido/intermediário da N-acetiltransferase 2 (OR combinada = 0,41; IC95%: 0,18-0,90). Há, portanto, evidências para subsidiar o manejo de RAM antituberculose nos serviços de saúde pública.

Descritores: Tuberculose; Efeitos colaterais e reações adversas relacionados a medicamentos; Antituberculosos; Revisão.

Introduction

There have been few technological advances in the treatment of tuberculosis (TB). First-line antituberculosis drugs (rifampin, isoniazid, pyrazinamide, and ethambutol) constitute the main therapeutic strategy to control the disease, their efficacy being greater than 95% in susceptible patients.[1]

The treatment regimen currently used in developing countries is a fixed-dose, single-tablet combination of four drugs (rifampin, isoniazid, pyrazinamide, and ethambutol) in the intensive phase of treatment in order to reduce primary resistance to the isoniazid-rifampin combination and improve patient adherence to treatment.[1,2] However, treatment discontinuation and dropout persist and result in increased morbidity and mortality from TB.[3,4]

Negative outcomes of TB treatment pose risks to individual and public health, prolonging the infection and thus increasing the possibility of transmission of multidrug-resistant bacilli. Therefore, factors associated with treatment failure have been studied in order to improve treatment and prognosis.[5]

Adverse drug reactions (ADRs) are defined by the World Health Organization.[6] The Brazilian

National Ministry of Health divides adverse reactions to antituberculosis drugs into two large groups on the basis of their severity. Minor adverse effects occur in 5-20% of cases and are thus classified because they require no immediate modification of the standard regimen and, in most cases, call for measures that can be taken at primary care clinics. Major adverse effects are less common; that is, they occur in 3-8% of cases and call for treatment discontinuation or modification, as well as specialized care.[1,7]

According to the Brazilian guidelines on TB, adverse reactions to antituberculosis drugs are multifactorial. However, the major determinants of adverse reactions to antituberculosis drugs are the doses, the time of day at which the drugs are administered, age (from the fourth decade of life onward), nutritional status (body weight loss > 15%), alcohol consumption (daily alcohol intake > 101 mL), liver function, kidney function, and co-infection with HIV.[1,8,9]

In recent decades, there has been an increasing concern over patient adherence to antituberculosis treatment.[10] Therefore, studies on this topic are warranted, given that adverse reactions during TB treatment are a major factor for treatment nonadherence. The objective of the present study was to identify scientific evidence on risk factors associated with adverse reactions to antituberculosis drugs.

Methods

This was a systematic review of studies retrieved from electronic databases and examining risk factors associated with adverse reactions to antituberculosis drugs. The LILACS database was searched for articles published between January of 1982 and April of 2013, and the MEDLINE database was searched for articles published between January of 1965 and April of 2013. The MEDLINE and LILACS databases were searched with the use of MeSH and DeCS terms, respectively, in combination with the appropriate Boolean operators (OR, AND, and NOT), as shown in Chart 1.

Because our database searches covered a long period, there was no need for cross-referencing. The LILACS database was concomitantly searched for articles, theses, and dissertations, articles being chosen whenever there was a duplicate entry.

The retrieved articles were initially screened by the reading of their titles and abstracts. The inclusion criteria were as follows: having an available abstract; having been published in English, Spanish, or Portuguese; being a study of humans only; being an original, quantitative study (i.e., systematic reviews, meta-analyses, and case reports being excluded); having included individuals over 10 years of age, given that the treatment regimen recommended for children differs from that recommended for adults; having included individuals with non-multidrug-resistant pulmonary TB caused by *Mycobacterium tuberculosis*, including those with latent TB; having involved at least one of the drugs that constitute the treatment regimen recommended by the World Health Organization and the Brazilian National Ministry of Health (i.e., rifampin, isoniazid, pyrazinamide, and ethambutol); and

Chart 1 – Search strategies used in order to retrieve articles from the databases.

Database	Search strategy
MEDLINE	(("tuberculosis, pulmonary"[MeSH Terms]) AND (("rifampin"[MeSH Terms] OR "rifampin"[All Fields]) OR ("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields]) OR ("pyrazinamide"[MeSH Terms] OR "pyrazinamide"[All Fields]) OR ("ethambutol"[MeSH Terms] OR "ethambutol"[All Fields]) OR ("antitubercular agents"[MeSH Terms] OR (("antitubercular"[All Fields]) AND drug[All Fields])) OR (RHZ[All Fields]) OR (RHZE[All Fields])) AND (("toxicity"[Subheading] OR "toxicity"[All Fields]) OR ("chemically induced"[Subheading] OR "chemically induced"[All Fields]) OR ("contraindic ations"[Subheading] OR "contraindications"[All Fields]) OR ("complications"[Subheading] OR "complications"[All Fields]) OR ("adverse effects"[Subheading] OR "adverse effects"[All Fields]) OR ("poisoning"[Subheading] OR "poisoning"[All Fields] OR "poisoning"[MeSH Terms])) AND (abstract[text] AND ("1982/01/01"[PDAT] : "2013/04/30"[PDAT]) AND "humans"[MeSH Terms] AND (English[lang] OR Portuguese[lang] OR Spanish[lang]) AND "adult"[MeSH Terms])
LILACS	"tuberculose pulmonar" [Descritor de assunto] and rifampicina or "isoniazida" or "pirazinamida" or "etambutol" or "drogas antituberculose" or "RHZ" or "RHZE" [Descritor de assunto] and "reacao adversa a medicamento" or "intoxicacao" or "toxicidade" or "/efeitos adversos" or efeito colateral [Palavras]

having described or referred to estimators of the association between ADRs and risk factors.

For each criterion, there were two response options: yes and no. In order to be included in the review, an article had to meet all of the inclusion criteria; that is, the response option for each of the aforementioned criteria had to be "yes". When there was uncertainty as to whether a given article met all of the inclusion criteria, the article in question was read in its entirety. A total of 85 articles (2 articles from the LILACS database and 83 articles from the MEDLINE database) were selected. Only 1 article was unavailable in full text.

In most of the studies, statistical associations between ADRs and their risk factors had not been calculated. Therefore, the data were processed with Epi Info, version 3.5.3, ORs being calculated as measures of association between risk factors and ADRs, with 95% CIs. In addition, Pearson's chi-square test (with Yates' correction) or two-tailed Fisher's exact test was used (n < 5). Meta-analyses were performed by means of the Mantel-Haenszel test and by calculating the combined OR (cOR). For all analyses, the level of significance was set at 5%.

Results

A total of 1,389 articles were retrieved. Of those, 20 were retrieved from the LILACS database and 1,369 were retrieved from the MEDLINE database. There were 2 duplicate studies. The duplicates were excluded from the analysis, and 1,387 studies were evaluated.

Eighty-four articles were selected to be read in their entirety by two independent raters, who took into account four criteria: 1) the study did include individuals over 10 years of age, given that most of the abstracts provided no such information; 2) the study examined adverse reactions to antituberculosis drugs using the terms ADR(s), side effect(s), toxicity, or adverse effect(s); 3) the study had a loss of less than 20% of the sample for the analyses of interest; and 4) the study included measures of association between ADRs and risk factors or allowed the calculation of such measures. In order to be included in the review, an article had to meet all four criteria.

A total of 68 articles were excluded. Of those, 21 were excluded for not meeting the inclusion criteria: much of the information that was unclear

in the abstracts was clarified only after the articles were read in their entirety; 14 were excluded because they included individuals under 10 years of age; 6 were excluded for not having described any adverse reaction to antituberculosis drugs; 21 were excluded because more than 20% of the sample was lost; and 6 were excluded for not including measures of association between ADRs and risk factors or for not including data that allowed the calculation of such measures. This resulted in the inclusion of 16 articles in the present review. The articles were selected with the aid of Microsoft Office Excel 2010, and the process is illustrated in Figure 1.

Most (63%) of the studies were conducted in Asia, 2 were conducted in Latin America, 2 were conducted in North America, 1 was conducted in Europe, and 1 was conducted in Africa. Table 1 presents the general characteristics of the studies included in the review.

Of the 16 studies included in the present review, 56% had been conducted in the past 10 years, and 4 had been conducted in the 1980s or 1990s. All of the studies were available in English. In addition, 63% had a longitudinal design, and only 2 were clinical trials.

The sample sizes were measured for the proposed designs. The smallest sample consisted of 100 individuals,[11,12] and the largest consisted of 908 individuals.[13]

Two studies involved individuals with latent TB receiving chemoprophylaxis. The treatment given to individuals with active TB varied across studies in terms of drugs, doses, frequency, and duration.

The age of the participants varied widely across studies, being unspecified in most.[14-20] Approximately 70% of the studies involved inpatients,[11,14-18,20-25] others involved outpatients,[21,26] and 1 involved an unspecified population.[19]

Statistical analysis revealed that the risk factors associated with adverse reactions to antituberculosis drugs were as follows: gender; race/ethnicity; nationality; age; weight; marital status; treatment regimen; genetic factors; anemia; co-infection with HIV, HBV, or HCV; diabetes; liver disease; hypoalbuminemia; hyponatremia; lymphopenia; and alcohol, tobacco, or illicit drug use.

Table 2 presents the risk factors that were significantly associated with ADRs. The ADRs were
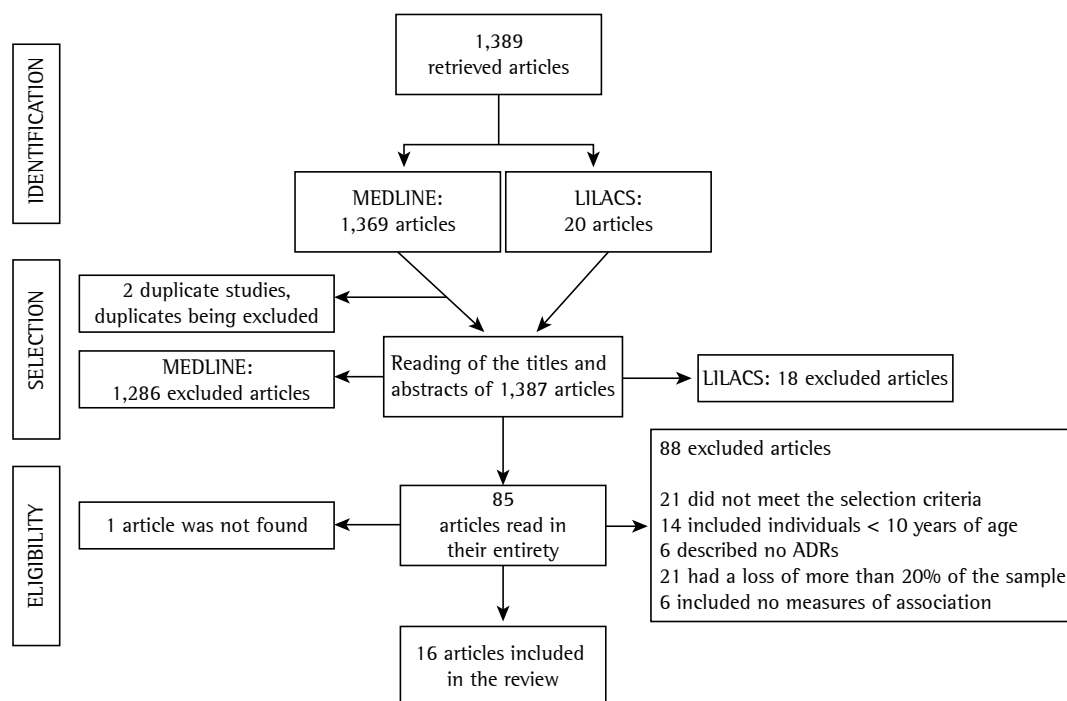
Figure 1 – Flowchart of article selection. ADRs: adverse drug reactions.

divided into gastrointestinal ADRs, neurological ADRs, immune-mediated ADRs, hepatic ADRs, and other ADRs.

Gastrointestinal ADRs included nausea, vomiting, indigestion, diarrhea, and other, unspecified, reactions. Co-infection with HIV was the only risk factor for gastrointestinal ADRs, with a significant association with the development of diarrhea.[20]

Neurological ADRs included vertigo and other, unspecified, reactions. However, no risk factors were significantly associated with neurological ADRs.

Immune-mediated ADRs included fever, herpes zoster, Kaposi's sarcoma, oral candidiasis, immune reconstitution inflammatory syndrome, and other, unspecified, reactions. Co-infection with HIV was found to be a risk factor for Kaposi's sarcoma and oral candidiasis.[20] Fever was a common ADR, being significantly associated with the following risk factors: anemia; hypoalbuminemia; hyponatremia; alcoholism; and co-infection with HIV.[16]

Hepatic ADRs were the most investigated ADRs, including jaundice, hepatitis, hepatotoxicity, and drug-induced hepatotoxicity. The rifampin-streptomycin-isoniazid-pyrazinamide combination taken daily for 3 months; the rifampin-streptomycin-isoniazid-pyrazinamide taken daily for 3 months, followed by the streptomycin-isoniazid-pyrazinamide combination taken twice a week for 2 months; and the streptomycin-isoniazid-pyrazinamide combination taken daily for 3 months, followed by the streptomycin-isoniazid-pyrazinamide combination taken twice a week for 2 months were compared and were found to be statistically significant protective factors for jaundice.[13] In addition, primary chemoprophylaxis was found to be a statistically significant protective factor for hepatotoxicity.[21]

The association between genetic factors and hepatic ADRs was evaluated in 5 studies. A slow N-acetyltransferase 2 (NAT2) acetylator phenotype was found to be a significant risk factor for hepatitis.[25] In contrast, a rapid/intermediate NAT2 acetylator phenotype was found to be a protective factor for hepatotoxicity.[11,18] In addition, a C/C genotype at rs2070401 in BACH1 and a G/A or A/A genotype at rs4720833 in MAFK were found to be risk factors for drug-induced hepatotoxicity.[12]

Only 3 studies showed a statistically significant association between sociodemographic factors and hepatic ADRs. One study showed that being under 65 years of age is a protective factor for hepatitis,[15] whereas another showed that

Table 1 – Studies included in the systematic review, conducted in the 1965-2012 period.

Author	Study design	Age group (years)	Sample (n)	Study population	Study period	Study setting	Treatment regimen	Statistical analysis
Ai et al.[14]	Case-control study	≤ 60 and > 60	639	Outpatients	June of 2006 to March of 2007	China	RHZE for 2 months + RH for 4 months	Unspecified univariate and multivariate analyses
Baghaei et al.[15]	Population-based cohort study	< 65 and ≥ 65	761	Inpatients	January of 2006 to January of 2008	Iran	RHZE for 6 months	X^2, Fisher's exact test, Mann-Whitney test, and logistic regression
Barnes et al.[16]	Cohort study	≥ 15	161	Inpatients	June of 1984 to March of 1985	USA	No data	X^2 and Fisher's exact test
Cantalice Filho et al.[17]	Case-control study	15-49 and ≥ 60	581	Inpatients	January of 1980 to December of 1996	Brazil	RHZ for 2 months + RH for 4 months	X^2 and Fisher's exact test
Cho et al.[18]	Cohort study	51.2 ± 17.5 46.7 ± 18.4	132	Inpatients	June of 2004 to December of 2005	South Korea	RHZE for 2 months + HRE for 4 months	Mann-Whitney test, X^2, and Fisher's exact test
HKCS/ BMRC[19]	Clinical trial	≥ 15	620	Unspecified	October of 1984 to October of 1986	China	SHRZ (3×/ week for 6 months)	Relative frequency (%) and absolute frequency (n), unspecified univariate analysis
Kelly et al.[20]	Cohort study	Mean, 34.9 and 41.7	187	Inpatients	November of 1991 to May of 1993	Africa	SHRZ for 2 months/ TH for 6 months	Kaplan-Meier method, unspecified univariate and multivariate analyses
Khalili et al.[11]	Case-control study	18-86	100	Inpatients	September of 2006 to March of 2009	Iran	RHZE for 2 months + RH for 4 months	X^2
Lee et al.[21]	Retrospective cohort study	18-84	148 (Latent TB)	Outpatients/ inpatients	April of 1999 to March of 2001	USA	RZ for 2 months	Relative frequency (%) and absolute frequency (n), relative risk, and multivariate analysis

Table 1 – Continued...

Author	Study design	Age group (years)	Sample (n)	Study population	Study period	Study setting	Treatment regimen	Statistical analysis
Nanashima et al.[12]	Randomized cross-sectional study	22-94	100	Inpatients	May of 2005 to September of 2006	Japan	H (400 mg/day) + R (450 mg/day)	Mann-Whitney test, X^2, Fisher's exact test, and logistic regression
Martínez Sanchis et al.[22]	Cohort study	≥ 10 to ≥ 64	198 (Latent TB)	Inpatients	December of 1996 to December of 2002	Spain	H 300 mg/day (2 or 6 months)	X^2, Fisher's exact test, and logistic regression
Sharma et al.[23]	Cohort study	16-80	346	Inpatients	1996-2000	India	RHZE	X^2 and logistic regression
Sirinak et al.[24]	Cohort study	≥ 18	769	Inpatients	May of 2005 to September of 2006	Thailand	RHZE	Unspecified univariate analysis and logistic regression
Teixeira et al.[25]	Case-control study	> 18	167	Inpatients	1998-2008	Brazil	H (400 mg/day) + others	Mann-Whitney test, X^2, Fisher's exact test, Student's t-test, etc.
Teleman et al.[26]	Retrospective cohort study	16-82	783	Outpatients	January of 1998 to December of 1998	Singapore	RHZ for 9 months + E or S	Mann-Whitney test, X^2, Fisher's exact test, and logistic regression
No authors listed[13]	Clinical trial	≥ 12	908	Outpatients	Unspecified	India	R3/R5/Z5	Relative frequency (%) and absolute frequency (n), unspecified univariate analysis

TB: tuberculosis; HKCS: Hong Kong Chest Service; BMRC: British Medical Research Council; R: rifampin; H: isoniazid; Z: pyrazinamide; E: ethambutol; S: streptomycin; T: thiocetazone; R3: rifampin-streptomycin-isoniazid-pyrazinamide daily for 3 months; R5: rifampin-streptomycin-isoniazid-pyrazinamide daily for 3 months, followed by streptomycin-isoniazid-pyrazinamide twice a week for 2 months; Z5: streptomycin-isoniazid-pyrazinamide daily for 3 months, followed by streptomycin-isoniazid-pyrazinamide twice a week for 2 months; and X^2: chi-square test.

being ≤ 60 years of age is a protective factor for drug-induced hepatotoxicity.[26] Being male was found to be a significant protective factor for hepatotoxicity.[21]

Other ADRs included arthralgia, exanthema, and unspecified reactions (kidney disorders, jaundice, hearing loss, liver problems, and skin rash). One study showed that age (< 60 years) was a significant protective factor for unspecified reactions.[14] The rifampin-streptomycin-isoniazid-pyrazinamide combination taken daily for 3 months and the rifampin-streptomycin-isoniazid-pyrazinamide taken daily for 3 months, followed by the streptomycin-isoniazid-pyrazinamide combination taken twice a week for 2 months were protective factors for arthralgia; in contrast,

Table 2 – Statistically significant associations between risk factors and adverse effects of antituberculosis drugs in the reviewed studies, conducted in the 1965-2013 period.

Author	Risk factor	ADR		OR	95% CI	X² (Yates' correction) or two-tailed Fisher's exact test	Value of p
Kelly et al.[20]	HIV Present Absent	Diarrhea + 42 10	Diarrhea – 83 52	2.63	1.17-6.37	5.461	0.019
Barnes et al.[16]	Hyponatremia Present Absent	Fever + 9 5	Fever – 22 51	16.6	3.95-146.80	Two-tailed Fisher's exact test	0.000
Barnes et al.[16]	Hypoalbuminemia Present Absent	Fever + 88 18	Fever – 24 30	6.11	2.74-13.68	23.545	0.000
Barnes et al.[16]	Alcoholism Present Absent	Fever < 7 days 10 4	Fever > 7 days 23 48	5.22	1.30-24.76	Two-tailed Fisher's exact test	0.014
Barnes et al.[16]	Anemia Present Absent	Fever < 7 days 14 0	Fever > 7 days 54 59	∞	3.3804 to ∞	Two-tailed Fisher's exact test	0.000
Barnes et al.[16]	Hyponatremia Present Absent	Fever < 7 days 9 5	Fever > 7 days 22 51	4.17	1.09-17.46	4.577	0.032
Barnes et al.[16]	Hypoalbuminemia Present Absent	Fever < 7 days 14 0	Fever > 7 days 54 19	∞	1.03 to ∞	Two-tailed Fisher's exact test	0.034
Kelly et al.[20]	HIV Present Absent	Fever + 69 20	Fever – 56 42	2.59	1.31-5.19	7.850	0.005
Kelly et al.[20]	HIV Present Absent	Oral candidiasis + 19 1	Oral candidiasis – 106 61	10.93	1.64-461.62	Two-tailed Fisher's exact test	0.004
Kelly et al.[20]	HIV Present Absent	Kaposi's sarcoma + 10 0	Kaposi's sarcoma – 115 62	∞	1.15 to ∞	Two-tailed Fisher's exact test	0.032
Ai et al.[14]	Age < 60 years > 60 years	ADR + 209 77	ADR – 288 65	0.61	0.41-0.91	6.136	0.013
Lee et al.[21]	Recent infection Present Absent	Hepatotoxicity + 13 1	Hepatotoxicity – 66 68	13.39	1.89-577.38	Two-tailed Fisher's exact test	0.002
No authors listed[13]	Therapeutic regimen R3 R5 and Z5	Jaundice + 18 328	Jaundice – 279 283	0.06	0.03-0.09	190.15	0.000
No authors listed[13]	Therapeutic regimen R5 R3 and Z5	Jaundice + 26 320	Jaundice – 281 281	0.08	0.05-0.13	170.83	0.000
No authors listed[13]	Therapeutic regimen Z5 R3 and R5	Jaundice + 2 344	Jaundice – 302 260	0.01	0.00-0.02	Two-tailed Fisher's exact test	0.000
Cho et al.[18]	NAT2 Rapid or intermediate acetylator Slow acetylator	Hepatotoxicity + 11 7	Hepatotoxicity – 102 12	0.18	0.05-0.68	7.977	0.005

Table 2 – Continued...

Author	Risk factor	ADR		OR	95% CI	X² (Yates' correction) or two-tailed Fisher's exact test	Value of p
Khalili et al.[11]	NAT2 Rapid or intermediate acetylator	Hepatotoxicity +	Hepatotoxicity −	0.09	0.02-0.46	10.322	0.001
		5	31				
	Slow acetylator	9	5				
Nanashima et al.[12]	C/C genotype at rs2070401 in BACH1 G/A or A/A genotype at rs4720833 in MAFK	Drug-induced hepatotoxicity +	Drug-induced hepatotoxicity −	9.73	2.04-90.86	Two-tailed Fisher's exact test	0.001
	Present	16	37				
	Absent	2	45				
Teixeira et al.[25]	NAT2 genotype	Hepatitis +	Hepatitis −	2.71	1.03-7.65	4.084	0.043
	Slow acetylator	18	64				
	Others	8	77				
Baghaei et al.[15]	Age	Hepatitis +	Hepatitis −	0.6	0.39-0.94	5.013	0.025
	< 65 years	50	416				
	≥ 65 years	49	246				
Teleman et al.[26]	Age	Drug-induced hepatotoxicity +	Drug-induced hepatotoxicity −	0.04	0.00-0.17	37.264	0.000
	≤ 60 years	26	613				
	> 60 years	29	368				
No authors listed[13]	Therapeutic regimen	Arthralgia +	Arthralgia −	0.66	0.49-0.88	8.164	0.004
	R3	137	160				
	R5 and Z5	345	266				
No authors listed[13]	Therapeutic regimen	Arthralgia +	Arthralgia −	0.55	0.41-0.74	17.158	0.000
	R5	133	174				
	R3 and Z5	349	252				
No authors listed[13]	Therapeutic regimen	Arthralgia +	Arthralgia −	2.85	2.11-3.87	49.89	0.000
	Z5	212	92				
	R3 and R5	270	334				

ADR: adverse drug reaction; X²: chi-square test; R3: rifampin-streptomycin-isoniazid-pyrazinamide daily for 3 months; R5: rifampin-streptomycin-isoniazid-pyrazinamide daily for 3 months, followed by streptomycin-isoniazid-pyrazinamide twice a week for 2 months; Z5: streptomycin-isoniazid-pyrazinamide daily for 3 months, followed by streptomycin-isoniazid-pyrazinamide twice a week for 2 months; and NAT2: N-acetyltransferase 2.

the streptomycin-isoniazid-pyrazinamide combination taken daily for 3 months, followed by the streptomycin-isoniazid-pyrazinamide combination taken twice a week for 2 months was a risk factor for arthralgia.[13]

The results of our meta-analyses (Figure 2) show that protective factors for hepatic ADRs include showing a rapid/intermediate NAT2 acetylator phenotype (cOR = 0.41; 95% CI: 0.18-0.90), being 35 years of age or older (cOR = 0.38; 95% CI: 0.20-0.72), and being male (cOR = 0.38; 95% CI: 0.20-0.72).

Discussion

In the present review, one study[13] demonstrated that a therapeutic regimen without rifampin was a risk factor for arthralgia. This finding suggests that rifampin can indirectly offer protection against arthralgia.

Joint pain is considered to be a minor side effect, and, when unrelated to hyperuricemia, it is frequently associated with pyrazinamide and, more rarely, isoniazid.[8] This is probably due to pyrazinoic acid, which is the major metabolite
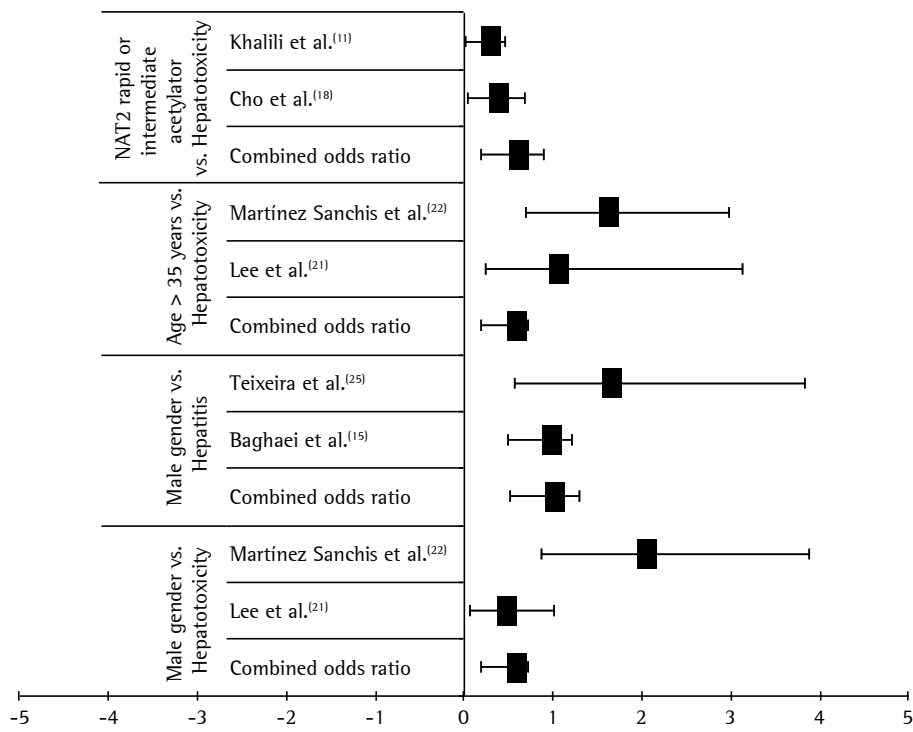
Figure 2 – Meta-analysis of the factors associated with hepatic adverse reactions to antituberculosis drugs.

of pyrazinamide; pyrazinoic acid inhibits renal tubular secretion of uric acid, thus increasing its serum concentration and causing joint pain.[7] In a multicenter study,[27] arthralgia was reported in 6 of 617 patients receiving rifampin, isoniazid, and pyrazinamide but in none of the 445 patients who received rifampin and isoniazid. However, most (87.5%) of the studies included in the present review involved different treatment regimens. Therefore, the results obtained by combining these studies can be misleading, and this is a limitation of our review.

The present review included 2 studies addressing latent TB rather than active TB. One of the studies[22] showed that primary chemoprophylaxis (the treatment of predisposed individuals in order to prevent TB infection, i.e., before they present with positive tuberculin skin test results) with 300 mg of isoniazid and 50 mg of pyridoxine for 2 months was a significant protective factor for hepatotoxicity when compared with secondary chemoprophylaxis (the treatment of latent TB infection, i.e., the treatment of patients with positive tuberculin skin test results without disease), which lasted longer (i.e., 6 months).

The duration of drug exposure can be a determinant of hepatic ADRs, given that longer exposure to toxic metabolites translates to a greater chance of severe injury. A study conducted in 2000 in Barcelona, Spain, showed that the duration of chemoprophylaxis was associated with toxic effects; however, it was impossible to establish a relationship with the type of drug used.[28]

There is divergence across studies regarding the association between HIV co-infection and ADRs during TB treatment.[10] In patients with TB/HIV co-infection, ADRs are generally related to the immune system itself[29] and are due to immunosuppression and drug metabolism pathways, which often generate toxic compounds. Therefore, the findings of one study,[20] in which HIV co-infection was considered a risk factor for diarrhea, are justifiable.

The interaction among antituberculosis drugs can potentiate their toxic effects on the gastrointestinal and hepatic systems.[22] Breen et al.[30] found no difference between groups of patients with and without HIV co-infection in terms of the incidence of hepatotoxicity. In another study,[29] co-infection with HIV was found to be a risk factor for grade 1 hepatotoxicity, defined as a three-fold increase in the lower limit of normal for alanine aminotransferase.

With regard to the use of alcohol, much of the alcohol ingested by humans is metabolized in the liver by the enzyme alcohol dehydrogenase. This enzyme converts alcohol to acetaldehyde, which has toxic effects even at reduced concentrations.[31,32] There is also evidence that the induction of cytochrome P450 2E1 by ethanol is related to the pathogenesis of alcoholic liver disease.[33] Coca[29] reported that alcoholism is a risk factor for hepatotoxicity. However, none of the studies examining alcohol use as a risk factor for hepatotoxicity showed a significant association between the two.

Being male was found to be significantly associated with hepatotoxicity, being a protective factor rather than a risk factor.[21] This is possibly due to the fact that androgen activity increases (induces) hepatic microsomal enzyme activity, which allows males to metabolize drugs more effectively.[31,34] However, further studies on gender-dependent variations in drug metabolism are needed in order to draw more definitive conclusions.

With regard to genetic factors, there was a significant association between a slow NAT2 acetylator phenotype—NAT2 being the principal enzyme responsible for metabolizing isoniazid—and hepatotoxicity,[11,18] given that this phenotype can generate more hepatotoxic metabolites.[31,35]

There is a possibility of information bias as a result of combining results of studies evaluating hepatotoxicity during antituberculosis treatment, given that several studies employ no criteria for determining the severity of hepatotoxicity, which can be classified as grade I, II, III, or IV hepatotoxicity on the basis of transaminase levels.[29] One limitation of the present study is that most of the reviewed studies presented no information regarding the diagnostic criteria for hepatotoxicity.

Gastrointestinal ADRs are the most common ADRs during TB treatment.[8] They might be due to the chemical effects of the antibacterial agents, which have an effect not only on bacterial cells but also on human cells.[31,36] They can therefore cause tissue damage in the central nervous system, peripheral nervous system, liver, and hematopoietic system.[37] However, in the present review, most of the risk factors for gastrointestinal ADRs were not significantly associated with such reactions.

Many (37.5%) of the reviewed studies evaluated the age of the participants; however, there were differences across studies in terms of age characterization, children and elderly individuals being evaluated. According to two studies,[14,15] elderly patients (over 60 or 65 years of age) are more likely to have ADRs. This is due to the fact that elderly individuals have a slower metabolism, which is due to reduced enzymatic activity, reduced hepatic clearance, and reduced availability of essential endogenous cofactors.[31,34] However, in one of the aforementioned studies,[14] the fact that the ADRs observed in the participants were not separately categorized limits this analysis. Another limitation is related to the results of two studies.[21,22] Although the combination of results was numerically significant in the meta-analysis, showing that being 35 years of age or older is a protective factor for hepatic ADRs in patients receiving TB treatment, it should be evaluated with caution, given that the authors' decision not to divide the participants into different population groups (e.g., elderly and non-elderly patients) is a confounding factor in the analysis of the results. The authors' decision was based on the small sample size, adults over 50 years of age constituting less than 15% of the sample.

The studies included in the present review were conducted in the 1986-2012 period, which is an extended period of time. The major drawback of early studies (i.e., those conducted in the 1980s or in the 1990s) was their lack of methodological rigor, with little or no information regarding sample size calculation, losses to follow-up, independent variables, statistical methods, ethical issues, and study population characteristics. Another problem is that, for none of the reviewed studies, the year of publication corresponded to the year in which the study had been conducted. Among researchers who study publication bias, some consider that the time elapsed between the completion of a study and its publication is an important factor and is related to results without statistical significance.[10]

Most of the studies included in the present review were observational studies. Only 2 clinical trials were included.[13,19] Observational studies are important because of their exploratory nature, which allows inferences to be made. However, a randomized clinical trial is the most appropriate study design to evaluate the safety profile of a given drug.[36,38]

Given that the incidence of TB is higher among poor individuals, we expected to find, among

the studies included in the present review, at least one in which socioeconomic factors, such as income and occupation, had been evaluated. However, none of the reviewed studies examined socioeconomic variables.

The highest TB incidence rates are concentrated in African countries. However, India, China, and Indonesia together accounted for more than 40% of all TB cases in 2006.[39] This explains why many (44%) of the studies included in the present review were conducted in the aforementioned countries.

The relationship between TB and socioeconomic indicators appears to be associated with the level of spatial aggregation and the particular characteristics of geographic areas.[40] In a study conducted in London, UK, it was found that for each 1% increase in the proportion of households with more than one person per room, the average TB notification rate increased by 12%.[41] However, the association between adverse reactions to antituberculosis drugs and socioeconomic factors has yet to be confirmed.

There is, however, an association between a low income and malnutrition, the latter being related to physiological changes. A low protein diet (poor nutrition) is related to changes in T-cell-mediated immune function, increasing susceptibility to *M. tuberculosis* infection and diseases.[40] This explains the results of one study,[16] in which albumin, iron, and sodium deficiency was a risk factor for fever, as was the use of alcohol.

ADRs are more closely monitored in a hospital setting, where complaints and symptoms are continuously monitored. In addition, the hospital setting allows fewer losses to follow-up and more detailed data collection in longitudinal studies.[13] In a study conducted in the outpatient clinic of a teaching hospital in the city of São Paulo, Brazil, the frequency of minor adverse reactions was 41.1% and that of major adverse reactions was 12.8%.[7] According to the authors of the study, the difference between their findings and those of other studies (in which the incidence was lower) might be due to the fact that patients treated at the outpatient clinic of the medical teaching hospital are routinely screened for all possible side effects. In the present review, most of the study populations consisted of inpatients. However, in several countries, the primary treatment regimens are delivered on an outpatient basis.[8]

It can be assumed that ADRs are underreported because of the difficulty in identifying such reactions and the difficulty in monitoring patients undergoing treatment. This limits the generalization of the results of the present study. Although patients are instructed to seek medical attention at a primary care clinic should any symptom arise, they rarely do in cases of mild ADRs. In addition, there is a long interval between medical visits, and ADRs are not usually reported or treated properly.

Another limitation of the present review is related to our methodological rigor; articles that did not meet all of the inclusion criteria were excluded from the review. In other reviews, rating scales are used in order to assist in the evaluation of the studies; therefore, rather than being excluded for not meeting methodological and statistical criteria, studies simply receive low ratings on these items.[42]

Although some of the risk factors analyzed in the present review were found to be significantly associated with ADRs, most of the results did not allow us to establish correlations, given that outcomes and exposure were defined differently across studies and therefore constituted an obstacle to our meta-analysis.

Final considerations

In the present review, ADRs were significantly associated with age, gender, treatment regimen, alcoholism, HIV co-infection, genetic factors, and nutritional deficiencies. Individual factors such as showing a rapid/intermediate NAT2 acetylator phenotype, being 35 years of age or older, and being male are protective factors for hepatic ADRs in patients receiving antituberculosis treatment. The remaining results should be interpreted cautiously, given that most of the data collected precluded a meta-analysis and, consequently, an evaluation of heterogeneity and external validity. The present systematic review can guide future studies aimed at achieving TB control for the benefit of public health.

References

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011.
2. Maciel EL, Guidoni LM, Favero JL, Hadad DJ, Molino LP, Jonhson JL, et al. Adverse effects of the new tuberculosis

treatment regimen recommended by the Brazilian Ministry of Health. J Bras Pneumol. 2010;36(2):232-8.

3. Awofeso N. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. Bull World Health Organ. 2008;86(3):B-D.

4. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.

5. Villa TC, Brunello ME, Arcêncio RA, Sassaki CM, Assis EG, Gonzalez RI. Factors predicting unfavorable results in tuberculosis treatment: an integrative literature review (2001-2005) [Article in Portuguese]. Online Braz J Nurs [serial on the Internet]. 2007 Oct [cited 2014 May 23];7(0):[about 13 p.]. Available from: http://www.objnursing.uff.br/index.php/nursing/article/view/1098

6. World Health Organization. The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: World Health Organization; 2002.

7. Vieira DE, Gomes M. Adverse effects of tuberculosis treatment: experience at an outpatient clinic of a teaching hospital in the city of São Paulo, Brazil. J Bras Pneumol. 2008;34(12):1049-55. http://dx.doi.org/10.1590/S1806-37132008001200010

8. Brasil. Ministério da Saúde. Secretaria de Políticas de Saúde. Departamento de Atenção Básica. Manual técnico para o controle da tuberculose: cadernos de atenção básica n°6. Brasília: Ministério da Saúde; 2002.

9. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48.

10. Brasil PE, Braga JU. Meta-analysis of factors related to health services that predict treatment default by tuberculosis patients. Cad Saude Publica. 2008;24 Suppl 4:s485-502. http://dx.doi.org/10.1590/S0102-311X2008001600003

11. Khalili H, Fouladdel S, Sistanizad M, Hajiabdolbaghi M, Azizi E. Association of N-acetyltransferase-2 genotypes and anti-tuberculosis induced liver injury; first case-controlled study from Iran. Curr Drug Saf. 2011;6(1):17-22. http://dx.doi.org/10.2174/157488611794479946

12. Nanashima K, Mawatari T, Tahara N, Higuchi N, Nakaura A, Inamine T, et al. Genetic variants in antioxidant pathway: risk factors for hepatotoxicity in tuberculosis patients. Tuberculosis (Edinb). 2012;92(3):253-9. http://dx.doi.org/10.1016/j.tube.2011.12.004

13. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. Am Rev Respir Dis. 1986;134(1):27-33.

14. Ai X, Men K, Guo L, Zhang T, Zhao Y, Sun X, et al. Factors associated with low cure rate of tuberculosis in remote poor areas of Shaanxi Province, China: a case control study. BMC Public Health. 2010;10:112. http://dx.doi.org/10.1186/1471-2458-10-112

15. Baghaei P, Tabarsi P, Chitsaz E, Saleh M, Marjani M, Shemirani S, el al. Incidence, clinical and epidemiological risk factors, and outcome of drug-induced hepatitis due to antituberculous agents in new tuberculosis cases. Am J Ther. 2010;17(1):17-22. http://dx.doi.org/10.1097/MJT.0b013e31818f9eae

16. Barnes PF, Chan LS, Wong SF. The course of fever during treatment of pulmonary tuberculosis. Tubercle. 1987;68(4):255-60. http://dx.doi.org/10.1016/0041-3879(87)90065-1

17. Cantalice Filho JP, Bóia MN, Sant Anna CC. Analysis of the treatment of pulmonary tuberculosis in elderly patients at a university hospital in Rio de Janeiro, Brazil. J Bras Pneumol. 2007;33(6):691-8. http://dx.doi.org/10.1590/S1806-37132007000600013

18. Cho HJ, Koh WJ, Ryu YJ, Ki CS, Nam MH, Kim JW, et al. Genetic polymorphisms of NAT2 and CYP2E1 associated with antituberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis. Tuberculosis (Edinb). 2007;87(6):551-6. http://dx.doi.org/10.1016/j.tube.2007.05.012

19. Hong Kong Chest Service/British Medical Research Council. Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. Am Rev Respir Dis. 1989;140(6):1618-22. http://dx.doi.org/10.1164/ajrccm/140.6.1618

20. Kelly PM, Cumming RG, Kaldor JM. HIV and tuberculosis in rural sub-Saharan Africa: a cohort study with two year follow-up. Trans R Soc Trop Med Hyg. 1999;93(3):287-93. http://dx.doi.org/10.1016/S0035-9203(99)90025-1

21. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. Int J Tuberc Lung Dis. 2002;6(11):995-1000.

22. Martínez Sanchís A, Calpe Calpe JL, Llavador Ros G, Ena Mu-oz J, Calpe Armero A. Primary prevention and treatment of latent tuberculosis infection with isoniazid: efficacy of a control program, 1997-2002 [Article in Spanish]. Arch Bronconeumol. 2005;41(1):27-33. http://dx.doi.org/10.1157/13070281

23. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med. 2002;166(7):916-9. http://dx.doi.org/10.1164/rccm.2108091

24. Sirinak C, Kittikraisak W, Pinjeesekikul D, Charusuntonsri P, Luanloed P, Srisuwanvilai LO, et al. Viral hepatitis and HIV-associated tuberculosis: risk factors and TB treatment outcomes in Thailand. BMC Public Health. 2008;8:245. http://dx.doi.org/10.1186/1471-2458-8-245

25. Teixeira RL, Morato RG, Cabello PH, Muniz LM, Moreira Ada S, Kritski AL, et al. Genetic polymorphisms of NAT2, CYP2E1 and GST enzymes and the occurrence of antituberculosis drug-induced hepatitis in Brazilian TB patients. Mem Inst Oswaldo Cruz. 2011;106(6):716-24. http://dx.doi.org/10.1590/S0074-02762011000600011

26. Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis. 2002;6(8):699-705.

27. Klasco RK (Ed): DRUGDEX® System. [database on the Internet]. Greenwood Village (CO): Thomson Micromedex. c1974-2012 - [cited 2014 May 23]. Available from: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/BAB6CF/DUPLICATIONSHIELDSYNC/B80A93/ND_PG/PRIH/ND_B/HCS/SBK/3/ND_P/Main/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/0028/ContentSetId/31/SearchTerm/isoniazid%20/SearchOption/BeginWith

28. Martínez Alfaro EM, Cuadra F, Solera J, Maciá MA, Geijo P, Sánchez Martínez PA, et al. Evaluation of 2 tuberculosis chemoprophylaxis regimens in patients infected with human immunodeficiency virus. The GECMEI Group

[Article in Spanish]. Med Clin (Barc). 2000;115(5):161-5. http://dx.doi.org/10.1016/S0025-7753(00)71496-5

29. Coca MN. Hepatotoxicidade ao esquema rifampicina, isoniazida e pirazinamida no tratamento da tuberculose em pacientes com e sem a síndrome da imunodeficiência humana adquirida [dissertation]. Dissertação (mestrado). Belo Horizonte: Faculdade de Medicina da Universidade Federal de Minas Gerais; 2009.

30. Breen RA, Miller RF, Gorsuch T, Smith CJ, Schwenk A, Holmes W, et al. Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax. 2006;61(9):791-4. http://dx.doi.org/10.1136/thx.2006.058867

31. Katzung BG. Farmacologia básica e clínica. 10th ed. São Paulo: McGraw Hill; 2010.

32. Mincis M, Mincis R. Doença hepática alcoólica. RBM [serial on the Internet]. 2010 Jun [cited 2014 May 23];67(1):21-31. Available from: http://www.moreirajr.com.br/revistas.asp?fase=r003&tid_materia=4336

33. Guengerich FP. Role of cytochrome P450 enzymes in drug-drug interactions. Adv Pharmacol. 1997;43:7-35. http://dx.doi.org/10.1016/S1054-3589(08)60200-8

34. Matos LC, Martins B. Hepatites tóxicas: revisão da literatura. Med Intern. 2005;4(12):239-58.

35. Possuelo LG. Estudo de polimorfismo presente no gene que codifica N- acetiltransferase 2 e associação com hepatotoxicidade em paciente com tuberculose tratados com RHZ [thesis]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2008.

36. Fuchs FD, Wannmacher L, Ferreira MB. Farmacologia Clínica: Fundamentos da terapêutica racional. 3rd ed. Rio de Janeiro: Guanabara Koogan; 2004.

37. Bisaglia JB, Santussi WM, Guedes AG, Gomes AP, Oliveira PC, Siqueira-Batista R. Atualização terapêutica em tuberculose: principais efeitos adversos dos fármacos. Bol. Pneumol Sanit. [serial on the Internet]. 2003 Dec [cited 2014 May 23];11(2):53-9. Available from: http://scielo.iec.pa.gov.br/scielo.php?script=sci_arttext&pid=S0103-460X2003000200008&lng=pt

38. Medronho RA. Epidemiologia. 2nd ed. São Paulo: Atheneu; 2009.

39. World Health Organization. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient. Geneva: World Health Organization; 2012.

40. San Pedro A, Oliveira RM. Tuberculosis and socioeconomic indicators: systematic review of the literature [Article in Portuguese]. Rev Panam Salud Publica. 2013;33(4):294-301. http://dx.doi.org/10.1590/S1020-49892013000400009

41. Mangtani P, Jolley DJ, Watson JM, Rodrigues LC. Socioeconomic deprivation and notification rates for tuberculosis in London during 1982-91. BMJ. 1995;310(6985):963-6. http://dx.doi.org/10.1136/bmj.310.6985.963

42. Sampaio RF, Mancini MC. Estudos de revisão sistemática: um guia para síntese criteriosa da evidência científica. Rev Bras Fisioter. [serial on the Internet]. 2007 Feb [cited 2014 May 23];1(11):83-9. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1413-35552007000100013

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Video-assisted thoracoscopic implantation of a diaphragmatic pacemaker in a child with tetraplegia: indications, technique, and results*

Implante de marca-passo diafragmático por videotoracoscopia em criança com tetraplegia: indicações, técnica e resultados

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Abstract

We report the case of a child with tetraplegia after cervical trauma, who subsequently underwent diaphragmatic pacemaker implantation. We reviewed the major indications for diaphragmatic pacing and the types of devices employed. We highlight the unequivocal benefit of diaphragmatic pacing in the social and educational reintegration of individuals with tetraplegia.

Keywords: Spinal cord injuries; Respiration, artificial; Pacemaker, artificial; Quadriplegia.

Resumo

Relatamos o caso de uma criança tetraplégica após trauma cervical que foi posteriormente submetida a implante de marca-passo diafragmático. Revisamos as principais indicações da estimulação diafragmática e os tipos de dispositivos empregados, assim como apontamos o inequívoco benefício da reinserção socioeducacional desses indivíduos na sociedade.

Descritores: Traumatismos da medula espinal; Respiração artificial; Marca-passo artificial; Quadriplegia.

Introduction

The generic term "diaphragmatic pacemaker" (DP) refers to a device that generates electrical impulses delivered to the phrenic nerve in order to produce diaphragm contractions that are aimed at replacing mechanical ventilation in patients with respiratory failure. The key requirement for the use of this treatment approach is that the phrenic nerve is preserved.

Electrical stimulation of the phrenic nerve was described 200 years ago, and, since then, this treatment approach has been investigated under various conditions, such as asphyxia, cholera, polio, and apnea.[1] However, the clinical use of DPs has occurred only in recent decades, after the study by Glenn & Phelps, who implanted a DP into patients with spinal trauma and congenital central hypoventilation syndrome.[2,3] Since then, there have been many advances in diaphragm pacing,

also referred to as electrical[4] or electrophrenic[5] ventilation.

There are two types of devices for stimulation of the phrenic nerve, depending on the site of implantation: directly on the phrenic nerve or directly on the diaphragm. Phrenic nerve pacemakers can be implanted on the nerve via the cervical or thoracic route. The phrenic nerve arises from the C3 and C4 nerve roots, and, more distally, from the C5 nerve root. When implantation is performed via the cervical route, there is the risk of the electrode being positioned on the nerve below its junction to the C5 nerve root. The presence of a tracheostomy can increase the risk of infection.[6] Therefore, the recommended site for implantation is the intrathoracic segment of the phrenic nerve, preferably by means of video-assisted thoracoscopic surgery.

In addition to implanting electrodes around the phrenic nerve, it is necessary to create a subcutaneous pocket to place a metallic extension of the electrode.

On the international market, there are two models of phrenic pacemakers: Mark IV® (Avery Biomedical Devices, Commack, NY, USA), which is monopolar (Figure 1),[7] and Atrostim® (Atrotech, Tampere, Finland), which is quadripolar.[8,9]

Another device that has been developed more recently is a true DP: NeuRx® (Synapse Biomedical, Oberlin, OH, USA).[10,11] This device is laparoscopically implanted directly on the motor point of the diaphragm. Although it has the theoretical advantage of being implanted via a single route, this device has one disadvantage: its electrodes are exteriorized through the skin of the patient.

Such types of pacemakers have been used in three groups of patients. The classic indication is patients with respiratory failure after spinal trauma or with respiratory failure due to central lesions caused by tumors or strokes. Another indication is patients with congenital central hypoventilation syndrome (Ondine syndrome),[12] particularly full-time ventilator-dependent patients, so that they can gain mobility during daytime. Finally, an indication that has yet to be proven is patients with amyotrophic lateral sclerosis, in the hope that DPs can delay the onset of respiratory failure.[13]

Considering that the use of electrical ventilation is still limited in Brazil, the objective of the present study was to report a case of DP implantation in a child with spinal trauma, not only to demonstrate the benefits obtained from this treatment option (essentially, the social reintegration of the patient and the technical ease of video-assisted thoracoscopic implantation) but also to demonstrate that DPs can be handled without difficulty even outside the hospital setting.

Case report

A five-year-old male patient from the city of Caxias do Sul, Brazil, presented with a history of pedestrian-motor vehicle accident (in January of 2010) and an upper cervical spine fracture, at C3-C4. The spinal cord injury was confirmed by axial CT and 3D reconstruction.

The patient underwent alignment and surgical fixation of the corresponding vertebrae. He developed tetraplegia and respiratory failure requiring full-time mechanical ventilation, and underwent tracheostomy, gastrostomy, and cystostomy. In addition to the clinical circumstances, social isolation was crucial to the family's decision to seek help. In social networks, his suffering was shared with other patients experiencing the same condition.

In April of 2013, implantation of a phrenic pacemaker was recommended. The preoperative evaluation included routine hematological tests, arterial blood gas analysis, and chest X-ray. A nerve conduction study of the phrenic nerve was requested in order to assess its functional viability, which could be impaired because of traumatic ischemia, as well as to evaluate phrenic nerve/diaphragm integrity, which is a key requirement for implantation. The nerve conduction study revealed proper nerve conduction, with a good response of the diaphragm to cervical transcutaneous electrical stimulation.

The surgical procedure for implantation of the device was conducted by the team of the Department of Thoracic Surgery of the General Hospital of the University of Caxias do Sul Foundation, in the city of Caxias do Sul, Brazil.

Because of the patient's specific clinical status, the anesthetic and surgical procedure demanded precautions that are unusual in young patients.[14] The patient was given general anesthesia with a tracheal tube inserted through the tracheostomy stoma, with the aid of bronchoscopy to achieve unilateral ventilation during the procedure. With the patient placed in the lateral decubitus position,

Figure 1 – Diaphragmatic pacemaker with the receiver connected to the electrode.

a 10-mm trocar was inserted in the midaxillary line, sixth intercostal space, for introduction of a fiber optic probe (30°). A 3-cm minithoracotomy was performed in the anterior axillary line, fourth intercostal space, for insertion of the components of the Mark IV® system and for phrenic nerve dissection.

Over the pericardium, the nerve was carefully dissected to prevent rupture or ischemia. The extent of dissection was kept as minimal as possible so that the electrode could "embrace" the nerve without causing excessive traction or compression (Figure 2). At this point, the system was connected, and DP stimulation was tested in vivo to confirm diaphragm contraction (Figure 3).

Through the minithoracotomy, over the pectoralis major muscle, a tunnel incision was made to create a subcutaneous pocket in which to place the device receiver, which was connected to the electrode implanted on the phrenic nerve. The system was tested again, under direct thoracoscopic visualization, using different voltages, to define the voltage that would produce an as-isometric-as-possible contraction bilaterally. Residual pneumothorax was evacuated by performing Valsalva maneuvers, without the need for pleural cavity drainage (Figure 3).

The possibility of performing the procedure by means of video-assisted thoracoscopic surgery reduced morbidity and accelerated postoperative recovery. The procedure was uneventful, and the patient was discharged on postoperative day 3.

Given that the use of mechanical ventilation leads to diaphragm atrophy with conversion of slow type I fibers to fast type II fibers,[15] after three weeks, which is the time required for surgical wound healing and for decrease in the edema at the nerve-electrode interface, the period of DP stimulation to condition the diaphragm was started.

Discussion

Although mechanical ventilation is the life-sustaining factor in patients with upper spinal trauma, it also has negative characteristics, such as diaphragm atrophy, barotrauma, tracheostomy and tube wounds, speech difficulty, loss of smell, etc. In addition, poorly ventilated posterior lung segments, impaired mucociliary clearance, and accumulation of excess secretion result in a high frequency of respiratory infections, which are the leading cause of death in such patients.[16]

Transition from the ventilator to the DP requires a systematic progression, both for the child, so that he/she can adapt as physiologically and comfortably as possible, and the caregiver, who should be able to identify signs of ventilatory effort and fatigue. The child's family was trained to recognize such signs and quickly proved to be able to handle the device.

Closure of the tracheostomy tube and perception of the diaphragm muscle contraction caused discomfort and anxiety, but such symptoms were addressed and were improved at each session of use of the equipment by the family itself.

It is known that, in diaphragm pacing with a DP, there is a relationship between stimulation with high frequencies and neural fatigue/degeneration. Initially, stimulation occurred at low frequencies (< 10 Hz) and at an RR of 12 to 15 breaths/min. Accordingly, time off the ventilator was gradually increased day by day, starting with a 5-minute session every hour.

Figure 2 – Photograph showing the time of implantation of the diaphragmatic pacemaker intraoperatively.

Figure 3 – Photograph showing the positioning of the receivers and antenna intraoperatively.

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Tracheostomized mechanically ventilated patients experience loss of smell, which prevents them from differentiating foods and recognizing their taste because of a shift in airflow caused by positive pressure. After initiation of ventilation with the DP, the patient regained normal olfactory function, which also represents a gain in quality of life.[17]

Dependence on mechanical ventilation and the consequent reduction in mobility, which leads to social isolation, are factors to be considered, especially because, in general, patients are young, previously healthy individuals who have been abruptly deprived of autonomy. Psychological trauma and hopelessness settle in and are issues that need to be addressed by a specialized team. In this scenario, the resumption of social and educational interaction is the most celebrated result of the procedure.

At this writing, the discharged patient is living in his home, where he receives supportive care from a multidisciplinary team, and has returned to regular classes and started going to the movies and on outings with friends and family.

More than one year after the procedure, the child already remains off mechanical ventilation for more than 10 uninterrupted hours, maintaining a satisfactory respiratory pattern (tidal volume = 277 mL; RR = 18 breath/min; and SpO_2 = 97%). Full-time pacing can be achieved.[18]

Although DPs are a technology that is still expensive in Brazil, they are available in the country, and medical industry and medical research point to an increase in the supply and quality of device options.

In conclusion, the possibility of dispensing with mechanical ventilation, even intermittently, allowing the reintegration of such individuals into society, as well as their inclusion in rehabilitation programs that are more effective and their return to school or work life, is the essence of this therapeutic indication.

References

1. Glenn WW, Phelps ML. Diaphragm pacing by electrical stimulation of the phrenic nerve. Neurosurgery. 1985;17(6):974-84. http://dx.doi.org/10.1227/00006123-198512000-00021

2. Glenn WW, Holcomb WG, Gee JB, Rath R. Central hypoventilation; long-term ventilatory assistance by radiofrequency electrophrenic respiration. Ann Surg. 1970;172(4):755-73. http://dx.doi.org/10.1097/00000658-197010000-00020

3. Glenn WW, Holcomb WG, McLaughlin AJ, O'Hare JM, Hogan JF, Yasuda R. Total ventilatory support in a quadriplegic patient with radiofrequency electrophrenic respiration. N Engl J Med. 1972;286(10):513-6. http://dx.doi.org/10.1056/NEJM197203092861004

4. Tedde ML, Onders RP, Teixeira MJ, Lage SG, Ballester G, Brotto MW, et al. Electric ventilation: indications for and technical aspects of diaphragm pacing stimulation surgical implantation. J Bras Pneumol. 2012;38(5):566-72. http://dx.doi.org/10.1590/S1806-37132012000500005

5. Stonnington HH. Electrophrenic respiration. Mayo Clin Proc. 1979;54(10):690.

6. Sardenberg RA, Secaf LB, Pinotti AC, Taricco MA, Brock RS, Younes RN. Diaphragmatic Pacing: unusual indication with successful application. J Bras Pneumol. 2011;37(5):697-9. http://dx.doi.org/10.1590/S1806-37132011000500020

7. Khong P, Lazzaro A, Mobbs R. Phrenic nerve stimulation: the Australian experience. J Clin Neurosci. 2010;17(2)205-8. http://dx.doi.org/10.1016/j.jocn.2009.06.012

8. Le Pimpec-Barthes F, Gonzalez-Bermejo J, Hubsch JP, Duguet A, Morélot-Panzini C, Riquet M, et al. Intrathoracic phrenic pacing: a 10-year experience in France. J Thorac Cardiovasc Surg. 2011;142(2):378-83. http://dx.doi.org/10.1016/j.jtcvs.2011.04.033

9. Hirschfeld S, Vieweg H, Schulz AP, Thietje R, Baer GA. Threshold currents of platinum electrodes used for functional electrical stimulation of the phrenic nerves for treatment of central apnea. Pacing Clin Electrophysiol. 2013;36(6):714-8. http://dx.doi.org/10.1111/pace.12073

10. Onders RP, Dimarco AF, Ignagni AR, Aiyar H, Mortimer JT. Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. Surgery. 2004;136(4):819-26. http://dx.doi.org/10.1016/j.surg.2004.06.030

11. Onders RP. Phrenic nerve and diaphragm motor point pacing. In: Patterson GA, Pearson FG, Cooper JD, Deslauriers J, Rice TW, Luketich JD, et al. editors. Pearson's Thoracic and Esophageal Surgery. 3rd ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2008. p. 1445-57. http://dx.doi.org/10.1016/B978-0-443-06861-4.50123-4

12. Weese-Mayer DE, Berry-Kravis EM, Ceccherini l, Keens TG, Loghmanee DA, Trang H; et al. An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med. 2010;181(6):626-44. http://dx.doi.org/10.1164/rccm.200807-1069ST

13. Onders RP, Elmo M, Kaplan C, Katirji B, Schilz R. Final analysis of the pilot trial of diaphragm pacing in amyotrophic lateral sclerosis with long-term follow-up: diaphragm pacing positively affects diaphragm respiration. Am J Surg. 2014;207(3):393-7. discussion 397.

14. Tedde ML, Vasconcelos Filho P, Hajjar LA, de Almeida JP, Flora GF, Okumura EM, et al. Diaphragmatic pacing stimulation in spinal cord injury: anesthetic and perioperative management. Clinics (Sao Paulo). 2012;67(11):1265-9 http://dx.doi.org/10.6061/clinics/2012(11)07

15. Ayas NT, McCool FD, Gore R, Lieberman SL, Brown R. Prevention of human diaphragm atrophy with short periods of electrical stimulation. Am J Respir Crit Care Med. 1999;159(6):2018-20. http://dx.doi.org/10.1164/ajrccm.159.6.9806147

16. University of Alabama at Birmighan. National Spinal Cord Injury Statistical Center [homepage on the Internet] Birminghan: NSCISC. [cited 2012 Nov 30]. 2012 Annual Report Complete Public Version. [Adobe Acrobat document,

104p. https://www.nscisc.uab.edu/PublicDocuments/reports/pdf/2012%20NSCISC%20Annual%20Statistical%20Report%20Complete%20Public%20Version.pdf

17. Adler D, J. Gonzalez-Bermejo J, Duguet A, Demoule A, Le Pimpec-Barthes F, Hurbault A, et al. Diaphragm pacing restores olfaction in tetraplegia.

Eur Respir J. 2009;34(2):365-70. http://dx.doi.org/10.1183/09031936.00177708

18. Glenn WW, Holcomb WG, Shaw RK, Hogan JF, Holschuh KR. Long-term ventilatory support by diaphragm pacing in quadriplegia. Ann Surg. 1976;183(5):566-77. http://dx.doi.org/10.1097/00000658-197605000-00014

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Nonadherence to treatment in lung transplant recipients: a matter of life and death

Falta de adesão ao tratamento em pacientes submetidos a transplante pulmonar: uma questão de vida ou morte

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To the Editor:

Lung transplantation is a complex intervention, requiring strict adherence to a very specific medical regimen, which involves not only drug taking but also a fairly restrictive daily routine. The extent to which patients adhere to the prescribed regimen plays a key role in achieving optimal transplantation outcomes.[1] Therefore, adherence to treatment is of great importance in the care of lung transplant recipients. The concept of adherence implies active participation by patients, who must understand their disease and the proposed treatment and strictly follow the recommendations of the health care team.[1] The World Health Organization proposes a close partnership among physicians, multidisciplinary staff, and patients, in order to improve treatment adherence.[2] The recent death of an adolescent female who underwent lung transplantation in the Lung Transplantation Department of the University of São Paulo School of Medicine *Hospital das Clínicas Instituto do Coração* (InCor, Heart Institute), located in the city of São Paulo, Brazil, and who died because of treatment nonadherence raised great concern about this issue, leading us to revise our multidisciplinary approach to patients and review the current knowledge of treatment adherence.

An 18-year-old female patient underwent double lung transplantation for end-stage cystic fibrosis. Initial immunosuppressive therapy included basiliximab and methylprednisolone, being followed by maintenance treatment with cyclosporine (adjusted to blood levels), mycophenolate, and prednisone. The patient remained stable for a period of one year and five months, after which she presented with acute progressive shortness of breath, hypoxemia, loss of lung function, and diffuse ground-glass opacities on HRCT

scans. Although her outpatient prescription drugs included cyclosporine, mycophenolate, prednisone, itraconazole, and trimethoprim-sulfamethoxazole, her cyclosporine blood levels were far below the minimum target. When queried, her caregiver admitted that, despite his efforts, she had not been taking her medication as prescribed in the past month and had been smoking narghile in her spare time. An open lung biopsy revealed grade A3 acute rejection, chronic airway rejection or bronchiolitis obliterans (C1), chronic vascular rejection (D), and organizing pneumonia. She was treated with rabbit antithymocyte globulin and corticosteroids but died as a result of alveolar hemorrhage and multiple infectious complications.

Recent studies have shown that as many as 25-50% of chronic disease patients can be considered nonadherers, nonadherence being temporary in some and permanent in others.[1,2] Among transplant recipients, nonadherence rates can be as high as 80%, especially in adolescent patients.[3] Although different methods and definitions of nonadherence (e.g., missed medication doses, delayed medication use, and dose modification) can influence the aforementioned rates,[1,4] nonadherence is undoubtedly an issue of great importance.

For lung transplant recipients, relief from the incapacitating symptoms of chronic lung disease comes at a price: long-term treatment; a complex therapeutic regimen; drug side effects; a restrictive diet; limited alcohol use; smoking cessation; and constraints on peer socialization. After the initial relief of the chronic symptoms, some patients lose the motivation to follow the strict rules required in order to maintain the graft. Therefore, the immediate relief (or alleviation of anxious feelings) can reduce or

negate the positive effects of long-term graft duration, in that it can lead to abandonment of the use of the prescribed medication. Special attention should be given to certain populations of lung transplant recipients. Being an adolescent is a predisposing factor for poor adherence to treatment because of the characteristic feeling of invulnerability in such individuals.[1] Most of the patients at our facility are cystic fibrosis patients, who are exactly in this age group and whose psychological profile increases the risk of nonadherence. However, noncompliance with physician recommendations cannot be understood simply as disobedience. Patients should not be coerced, made to feel guilty, or punished, the staff remaining in the comfortable position that it is up to patients to do exactly as they are told. Blaming patients for losing their graft because of nonadherence is not the correct way to deal with the situation. Health professionals should be trained in adherence assessment and management, because communication skills training with a focus on adherence management results in significantly higher adherence rates.[3,5]

Environmental factors that affect the extent to which patients will adhere to the recommended treatment should be identified.[5,6] Notable among such factors are patient beliefs regarding their disease and its treatment; transient emotional and cognitive problems; the quality of social support received; and an established relationship with the health care team.[5] Strategies to improve patient adherence to the therapeutic regimen should be implemented on the basis of individual characteristics and needs.[5] Finally, the health care team and patients should form a cohesive group.

Given that treatment nonadherence is a complex and multidimensional problem, none of the aforementioned efforts will ever produce a one-size-fits-all solution to nonadherence. Nevertheless, transplant teams should routinely revise and improve their multidisciplinary approach to patients. Further research and education are needed in order to gain a better understanding of how patient characteristics affect adherence to treatment.

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References

1. Korb-Savoldelli V, Sabatier B, Gillaizeau F, Guillemain R, Prognon P, Bégué D, et al. Non-adherence with drug treatment after heart or lung transplantation in adults: a systematic review. Patient Educ Couns. 2010;81(2):148-54. http://dx.doi.org/10.1016/j.pec.2010.04.013

2. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: WHO; 2003.

3. Dobbels F, Hames A, Aujoulat I, Heaton N, Samyn M. Should we retransplant a patient who is non-adherent? A literature review and critical reflection. Pediatr Transplant. 2012;16(1):4-11. http://dx.doi.org/10.1111/j.1399-3046.2011.01633.x

4. Germani G, Lazzaro S, Gnoato F, Senzolo M, Borella V, Rupolo G, et al. Nonadherent behaviors after solid organ transplantation. Transplant Proc. 2011;43(1):318-23. http://dx.doi.org/10.1016/j.transproceed.2010.09.103

5. Moraes AB, Rolim GS, Costa Jr AL. O processo de adesão numa perspectiva analítico comportamental. Rev Bras Ter Comp Cogn. 2009;11(2):329-45.

6. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its implications in transplant recipients. Drugs. 2007;67(10):1463-81. http://dx.doi.org/10.2165/00003495-200767100-00007

Anxiety, depression, and motivation for smoking cessation in hospitalized patients with and without cancer

Motivação para cessação do tabagismo, ansiedade e depressão em pacientes internados com e sem neoplasia

Igor Bastos Polônio, Meiryelle Landim Franco,
Marina Angélica Mendes Tegon, Célia Beatriz Gianotti Antoneli

To the Editor,

We read with interest the article by Almeida et al.[1] published in the Brazilian Journal of Pulmonology. The article addressed smoking habits and nicotine dependence in patients with head and neck cancer. Most of the patients showed high or very high nicotine dependence, and patients with advanced cancer smoked more cigarettes per day than did those with initial cancer, a finding that is paradoxical. However, this reveals the behavior of that specific population, despite their severe disease.

The importance of that finding is that smoking is a chronic disease characterized by nicotine dependence and, therefore, it is included in the International Classification of Diseases.[2] Smoking is one of the major risk factors for the development of various types of cancer. It is estimated that approximately 30% of all malignant tumors are associated with tobacco consumption. In patients with a diagnosis of cancer, smoking accounts for poor response to treatment, decreased survival and quality of life, toxicity to treatment, increased cancer recurrence, and the appearance of metastases. Smoking cessation treatment in this population is extremely difficult, because this population requires specific counseling, psychotherapy, and behavioral intervention, given that recurrence of smoking is very high and pharmacological treatment is not sufficient to maintain patient abstinence for long periods.[3] Consequently, knowing the profile of smokers with cancer is essential to the development of specific strategies for smoking cessation in this population. For this reason, we conducted a prospective observational study involving 50 individuals (smokers, former smokers, and nonsmokers) hospitalized in the clinical medicine ward of a tertiary hospital in the city of São Paulo, Brazil, between February and May of 2014. To that end, the following

instruments were administered: the Fagerström Test for Nicotine Dependence[4]; the Prochaska & DiClemente Stages of Change Model[5]; and the Hospital Anxiety and Depression Scale.[6] The study was approved by the Human Research Ethics Committee of the Anhembi Morumbi University, located in the city of São Paulo. Of the 50 respondents, 18 (36%) reported being nonsmokers, 15 (30%) reported being former smokers, and 17 (34%) reported being smokers. Therefore, most of the individuals analyzed have or have had tobacco exposure. Regarding the sociodemographic profile of the participants, we found that most were male and married and had a low level of education. As for age at smoking initiation, the present study corroborates the findings of previous studies,[7] showing that smoking initiation occurs during adolescence, with 58.3% of smokers having started smoking before the age of 18 years, which indicates the need for campaigns, specifically targeted at this age group, to raise awareness of the harmful effects of smoking among adolescents and young adults. One ethnographic study[8] reported that health concerns are the major motivating factor for smoking cessation. Most of the former smokers (72%) in the present study reported having quit smoking of their own volition, regardless of health problems, which suggests that further research on the subject is needed.

According to Table 1, the sample was homogeneous with regard to gender and age, without statistically significant differences. For statistical analysis, we chose to group smokers and former smokers together, given that former smokers remain at an increased risk for cancer for several years after smoking cessation. In the groups with and without cancer, there were 7 and 8 smokers, respectively. Most of the individuals showed moderate dependence according to

Table 1 – Demographic data as well as data for the Hospital Anxiety and Depression Scale and the Fagerström Test for Nicotine Dependence.

Variable	Smokers and former smokers (n = 31)				p[*]
	With cancer (n = 19)		Without cancer (n = 12)		
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Age	59.8 (9.8)	59 (34-80)	59.8 (17.8)	61.5 (25-81)	0.623
M/F[a]	12/7	(63.2/36.8)	11/1	(91.7/8.3)	0.086[†]
Anxiety	7.2 (4.0)	7.0 (2-15)	4.9 (2.4)	4.0 (2-10)	0.111
Depression	3.9 (3.5)	2.0 (0-13)	2.9 (2.0)	3.0 (0-6)	0.609
Fagerström	4.8 (2.0)	6.0 (1-7)	5.2 (1.5)	5.0 (3-7)	0.804

M/F: male/female. [a]Values expressed as n/n (%/%). *Mann-Whitney test. [†]Fisher's exact test.

the Fagerström Test for Nicotine Dependence[4] (70.6% of the smokers), and none showed high dependence. There were no significant differences in terms of anxiety or depression between the two groups analyzed. We expected that, in the patients with cancer, the levels of anxiety and depression would be higher[9]; however, many were in the end stage of the disease and were probably resigned. All of the patients with cancer knew their diagnosis. Regarding anxiety, as determined by the Hospital Anxiety and Depression Scale[6], 83% of the nonsmokers had scores indicating possible anxiety, whereas among smokers and former smokers, scores indicating unlikely anxiety were obtained in 65.6% of the cases. The statistical association was significant, suggesting that nonsmokers were possibly more anxious. Anxiety and depression are known to be greater in smokers.[2,10] Our results could be explained by the possible use of antidepressant and anxiolytic medications by the population of smokers and former smokers. The scale also addresses issues related to depression. In our sample, most of the nonsmokers (72%) and smokers (94%) had scores indicating unlikely depression.

According to Table 2, 86.6% of the smokers were in the precontemplation stage of change, whereas 13.4% were in the contemplation stage of change. Among those with cancer, 6 and 1 were in the precontemplation and contemplation stages of change, respectively. Among those without cancer, all were in the precontemplation stage of change. This finding is very interesting, given that these patients, many of whom had severe disease, were not thinking about quitting smoking (precontemplation stage of change). This shows the importance of the approach of physicians during hospitalization, providing clear information about the risks of smoking and offering specific treatment. It also indicates the need for

Table 2 – Stages of change in 15 smokers as per the Prochaska & DiClemente Stages of Change Model.

Stage of change	Smokers	
	n	%
Precontemplation	13	86.6%
Contemplation	2	13.4%

public health interventions specifically targeted at this population.

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References

1. Almeida AA, Bandeira CM, Gonçalves AJ, Araújo AJ. Nicotine dependence and smoking habits in patients with

head and neck cancer. J Bras Pneumol. 2014;40(3):286-93. http://dx.doi.org/10.1590/S1806-37132014000300012

2. Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, et al. Treating tobacco use and dependence. Clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; 2000.

3. Toll BA, Brandon TH, Gritz ER, Warren GW, Herbst RS; AACR Subcommittee on Tobacco and Cancer. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Clin Cancer Res. 2013;19(8):1941-8. http://dx.doi.org/10.1158/1078-0432.CCR-13-0666

4. Fagerström KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerström Tolerance Questionnaire. J Behav Med. 1989;12(2):159-82. http://dx.doi.org/10.1007/BF00846549

5. DiClemente CC, Prochaska JO. Self-change and therapy change of smoking behavior: a comparison of processes of change in cessation and maintenance. Addict Behav.1982;7(2):133-42. http://dx.doi.org/10.1016/0306-4603(82)90038-7

6. Castro MM, Quarantini L, Batista-Neves S, Kraychete D, Daltro C, Miranda-Scippa A. Validity of the hospital anxiety and depression scale in patients with chronic pain [article in Portuguese]. Rev Bras Anestesiol. 2006;56(5):470-7.

7. Corrêa PC. Tabagismo, hipertensão e diabetes - reflexões. Rev Bras Clin Terap. 2003;29(1):19-24.

8. Falcão TJ, Costa Ido C. Smoking in a small city: an ethnographic study to serve as a base for the creation of a public health program. J Bras Pneumol. 2008;34(2):91-7.

9. Jadoon NA, Munir W, Shahzad MA, Choudhry ZS. Assessment of depression and anxiety in adult cancer outpatients: a cross-sectional study. BMC Cancer. 2010;10:594. http://dx.doi.org/10.1186/1471-2407-10-594

10. Goodwin RD, Wall MM, Choo T, Galea S, Horowitz J, Nomura Y, et al. Changes in the prevalence of mood and anxiety disorders among male and female current smokers in the United States: 1990-2001. Ann Epidemiol. 2014;24(7):493-7. http://dx.doi.org/10.1016/j.annepidem.2014.01.014

Incidence of spontaneous subdural hematoma in incident cases of pulmonary arterial hypertension: a registry of cases occurring over a five-year period

Incidência de hematomas subdurais espontâneos em casos de pacientes com hipertensão arterial pulmonar: análise de um registro de cinco anos

Luis Felipe Lopes Prada, Francisca Gavilanes, Rogério Souza

To the Editor:

Imatinib, a tyrosine-kinase inhibitor, has recently been tested to determine its safety and efficacy for the treatment of pulmonary arterial hypertension (PAH), specifically in a study entitled Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES).[1] Experimental data suggest that imatinib plays a role in controlling pulmonary vascular remodeling, and this hypothesis had been previously tested in isolated case reports.[2] Nevertheless, the results of the IMPRES, a randomized, double-blind, placebo-controlled trial of imatinib mesylate as add-on therapy for pulmonary arterial hypertension, clearly demonstrated an increase in the occurrence of one severe side effect—spontaneous subdural hematoma.[1] The authors reported eight separate cases in which patients developed spontaneous subdural hematoma: two during the core study (in which 103 patients were enrolled in the treatment group) and six during the open-label, long-term extension study (in which 144 patients opted to be treated with imatinib). All of the patients were using oral anticoagulants at target levels.

In patients with chronic myeloid leukemia, the first study to investigate the efficacy of imatinib showed no spontaneous subdural hematoma but did identify thrombocytopenia in 4-24% of the patients, depending on the dosage.[3] After the use of imatinib became widespread, there were some reports of spontaneous bleeding and (more rarely) spontaneous subdural hematoma.[4]

A recent review of two randomized controlled trials of targeted therapies in PAH, collectively involving 564 patients, reported the occurrence of two events of spontaneous subdural hematoma among those patients, which translates to an incidence of 0.3% (95% CI: 0.1-1.3).[5] In both of those cases, the patients were using oral anticoagulants. The risk of bleeding in PAH patients was further evaluated in a study involving 218 patients with chronic thromboembolic pulmonary hypertension, connective tissue disease-associated PAH, and idiopathic PAH.[6] All of the patients evaluated in that study were receiving vitamin K antagonists. The authors found that the incidence of bleeding was highest in the patients with connective tissue disease-associated PAH, although central nervous system bleeding occurred in only one case (0.4%).

We have recently created a registry of incident cases of PAH treated at a large referral center in Brazil over a five-year period (2008-2013).[7,8] During that period, 178 newly diagnosed cases were included in the registry. During follow-up, two patients presented with spontaneous subdural hematoma, corresponding to an incidence of 1.1% (95% CI: 0.3-4.0): one was a female patient with idiopathic PAH (baseline mean pulmonary artery pressure of 50 mmHg; cardiac output of 4.3 L/min) who was using bosentan, and one was a male patient with schistosomiasis-associated PAH (baseline mean pulmonary artery pressure of 55 mmHg; cardiac output of 2.71 L/min) who was using sildenafil. Neither of those patients were using an oral anticoagulant.

Our data provide the first prospectively collected data on the incidence of spontaneous subdural hematoma in patients with PAH managed at a tertiary referral center. Our results underscore the assertion that the events reported in the IMPRES are not trivial and truly represent a major cause for concern regarding the safety of imatinib for use in PAH.

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References

1. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, et al. Imatinib Mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 2013;127(10):1128-38. http://dx.doi.org/10.1161/CIRCULATIONAHA.112.000765

2. Souza R, Sitbon O, Parent F, Simonneau G, Humbert M. Long term imatinib treatment in pulmonary arterial hypertension. Thorax. 2006;61(8):736. http://dx.doi.org/10.1136/thx.2006.064097

3. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14);1031-7. http://dx.doi.org/10.1056/NEJM200104053441401

4. Song KW, Rifkind J, Al-Beirouti B, Yee K, McCrae J, Messner HA, et al. Subdural hematomas during CML therapy with imatinib mesylate. Leuk Lymphoma. 2004;45(8):1633-6. http://dx.doi.org/10.1080/10428 190310001615666

5. Simonneau G, Hwang LJ, Teal S, Galie N. Incidence of subdural hematoma in patients with pulmonary arterial hypertension (PAH) in two randomized controlled clinical trials. Eur Respir J. 2012;40(suppl 56):941.

6. Henkens IR, Hazenoot T, Boonstra A, Huisman MV, Vonk-Noordegraaf A. Major bleeding with vitamin K antagonist anticoagulants in pulmonary hypertension. Eur Respir J. 2013;41(4):872-8. http://dx.doi.org/10.1183/09031936.00039212

7. Alves JL Jr, Gavilanes F, Jardim C, Fernandes CJ, Morinaga LT, Dias B, et al. Pulmonary arterial hypertension in the southern hemisphere: results from a registry of incident Brazilian cases. Chest. 2014 Oct 9. [Epub ahead of print] http://dx.doi.org/10.1378/chest.14-1036

8. Gavilanes F, Alves JL Jr, Fernandes C, Prada LF, Jardim CV, Morinaga LT, et al. Left ventricular dysfunction in patients with suspected pulmonary arterial hypertension. J Bras Pneumol. 2014;40(6):609-16. http://dx.doi.org/10.1590/S1806-37132014000600004

Hibernoma: an uncommon cause of a pleural mass

Hibernoma: uma causa incomum de massa pleural

Edson Marchiori, Gláucia Zanetti, Bruno Hochhegger

To the Editor:

Here, we report the case of a 37-year-old asymptomatic male patient who was referred because of abnormalities seen on a routine chest X-ray. The physical examination findings and laboratory test results were normal. A new chest X-ray revealed a large opacity in the left lower hemithorax. Chest CT revealed a heterogeneous pleural mass in the left lower hemithorax (Fig. 1). The mass appeared to be an extrapulmonary lesion arising from the chest wall. There were no calcifications. Complete surgical excision was performed. The gross specimen showed a well-circumscribed, encapsulated, soft, brown-to-yellow mass, measuring 10 × 9 × 5 cm (Fig. 2A). The microscopic findings were diagnostic of a hibernoma (Fig. 2B). At this writing, the patient remains asymptomatic and subsequent follow-up evaluations have been unremarkable.

Hibernomas are rare benign tumors that take their name from their histological similarity to the brown fat of hibernating animals, but also seen in the human fetus and to a diminishing degree with age in adults.[1-3] The distribution of this tumor follows the sites of persistence of brown fat. The
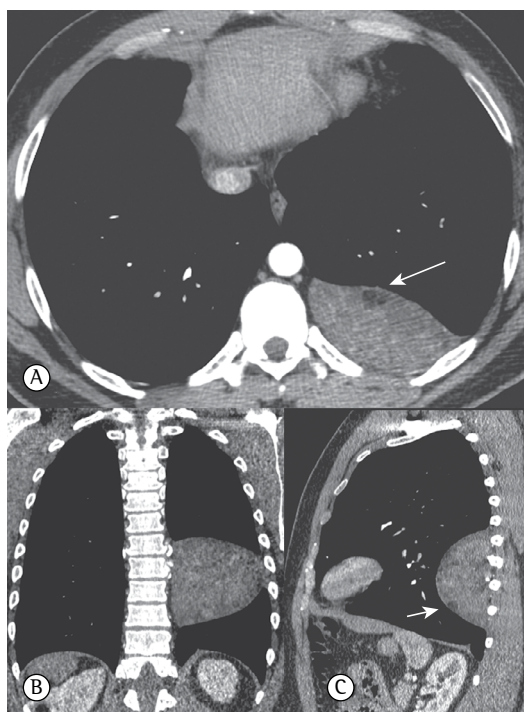
Figure 1 – Chest CT reconstructions in the axial, coronal, and sagittal planes (A, B, and C, respectively), showing a heterogeneous pleural mass with areas of low-attenuation (fatty tissue, arrows) in the left lower hemithorax.
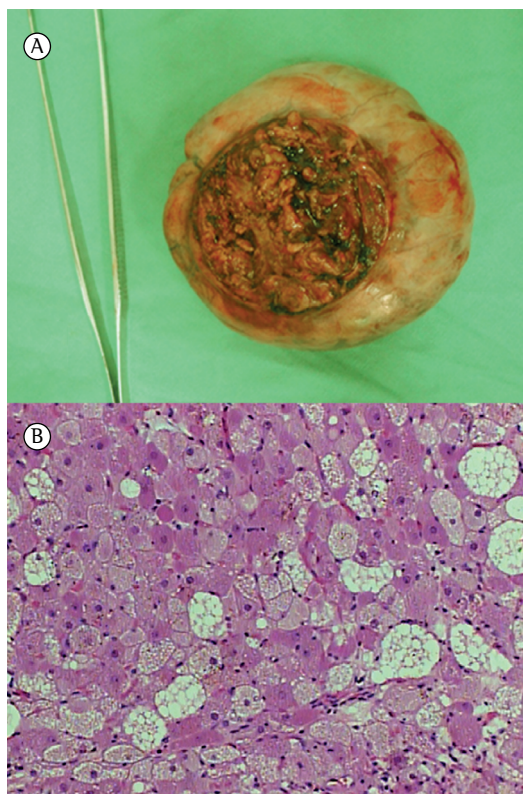
Figure 2 – Photograph of the gross specimen (A), demonstrating a well-circumscribed, encapsulated, soft, brown-to-yellow mass measuring 10 × 9 × 5 cm. Below, the photomicrograph (B) shows that, histologically, the tumor consisted of two tumor cell types: cells with granular intense eosinophilic cytoplasm; and clear multivacuolated cells filled with lipid droplets, with no evidence of cellular atypia or mitosis (hematoxylin and eosin staining; magnification, ×200).

most common sites are the thigh, shoulder, back, neck, thorax, upper extremity, abdomen, and retroperitoneum. Intrathoracic locations include the mediastinum and the pericardium. Tumors involving the pleura are extremely uncommon. In most cases, a hibernoma manifests as a painless mass and is an incidental finding on physical examination or imaging. Although these tumors are always benign, they tend to grow to large sizes and symptoms can arise from the compression of adjacent structures. In individuals with a hibernoma, significant weight loss has been described and is attributed to excessive thermogenesis of the tumor tissue responsible for the catabolism of circulating lipids and carbohydrates into thermal energy.[4] Complete surgical excision is the treatment of choice, and the postoperative prognosis is excellent. There have been no reports of recurrence or metastatic disease in hibernoma patients.[1,2] The gross specimen typically shows a well-encapsulated, firm, tan or brown tumor. Microscopy reveals univacuolated or multivacuolated fat cells with small, central nucleoli.[1]

On CT scans, a hibernoma usually presents as a heterogenous low-attenuation mass (with regions of fat and soft tissue attenuation); on T1- and T2-weighted magnetic resonance imaging, it is seen as a hyperintense, heterogeneous mass. In imaging studies, the main differential diagnoses are lipoma and liposarcoma. Because of the similarity of their fat content, hibernomas and lipomas have comparable signal characteristics on magnetic resonance imaging and CT scans. Although hibernomas are more heterogeneous due to their different composition, in terms of their fibrous and vascular elements, histopathological analysis is always necessary in order to make an accurate diagnosis.[1,2]

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References

1. Little BP, Fintelmann FJ, Mino-Kenudson M, Lanuti M, Shepard JA, Digumarthy SR. Intrathoracic hibernoma: a case with multimodality imaging correlation. J Thorac Imaging. 2011;26(2):W20-2. http://dx.doi.org/10.1097/RTI.0b013e3181e35acd

2. Ugalde PA, Guilbault F, Vaillancourt R, Couture C. Subpleural hibernoma. Ann Thorac Surg 2007;84(4):1376-8. http://dx.doi.org/10.1016/j.athoracsur.2007.05.044

3. Kumazoe H, Nagamatsu Y, Nishi T, Kimura YN, Nakazono T, Kudo S. Dumbbell-shaped thoracic hibernoma: computed tomography and magnetic resonance imaging findings. Jpn J Radiol. 2009;27(1):37-40. http://dx.doi.org/10.1007/s11604-008-0289-9

4. Hertoghs M, Van Schil P, Rutsaert R, Van Marck E, Vallaeys J. Intrathoracic hibernoma: report of two cases. Lung Cancer. 2009;64(3):367-70. http://dx.doi.org/10.1016/j.lungcan.2008.11.003

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Original articles: For original articles, the text (excluding the title page, abstracts, references, tables, figures and figure legends) should consist of 2000 to 3000 words. Tables and figures should be limited to a total of five. The

number of references should not exceed 30. Original articles should be divided into the following sections: Introduction, Methods, Results, Discussion, Acknowledgments, and References. The Methods section should include a statement attesting to the fact the study has been approved by the ethics in human research committee or the ethics in animal research committee of the governing institution. There should also be a section describing the statistical analysis employed, with the respective references. In the Methods and Results sections, subheadings may be used, provided that they are limited to a reasonable number. Subheadings may not be used in the Introduction or Discussion.

Review and Update articles: Review and Update articles are written at the request of the Editorial Board, which may occasionally accept unsolicited manuscripts that are deemed to be of great interest. The text should not exceed 5000 words, excluding references and illustrations (figures or tables). The total number of illustrations should not exceed eight. The number of references should not exceed 60.

Pictorial essays: Pictorial essays are also submitted only at the request of the Editors or after the authors have consulted and been granted permission by the Editorial Board. The text accompanying such essays should not exceed 3000 words, excluding the references and tables. No more than 12 illustrations (figures and tables) may be used, and the number of references may not exceed 30.

Case Reports: Case Reports should not exceed 1500 words, excluding title page, abstract, references and illustrations. The text should be composed of: Introduction, Case Report, Discussion and References. It is recommended that any and all information that might identify the patient be withheld, and that only those laboratory exams that are important for the diagnosis and discussion be presented. The total number of illustrations (figures or tables) should not exceed three, and the number of references should be limited to 20. When the number of cases presented exceeds three, the manuscript will be classified as a Case Series, and the same rules applicable to an original article will be applied.

Brief Communications: Brief communications should not exceed 1500 words, excluding references and tables. The total number of tables and figures should not exceed two, and the references should be limited to 20. The text should be unstructured.

Letters to the Editor: Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples:

Journal Articles

1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

Abstracts

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

Chapter in a Book

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

Official Publications

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Theses

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.