SPECIAL ARTICLE

The Archivos Archive, 2006: An Overview of Research Published in *Archivos de Bronconeumología*

José Ignacio de Granda Orive and Javier Jareño Esteban

Servicio de Neumología, Hospital Central de la Defensa Gómez Ulla, Madrid, Spain

Introduction

There is no doubt about the importance of respiratory medicine in current research, and the recent sharp increase in output is important not only from a scientific standpoint but also because of the impact of the work being carried out and published.[1-5] In an analysis of worldwide research output in respiratory medicine for the period 1996-2001, Rippon et al[6] indexed a total of 81 419 documents using the Science Citation Index and found that Finland, Canada, Spain, and the United Kingdom were countries of some importance in this field. Spain was particularly productive in the area of the pulmonary manifestations of the human immunodeficiency virus and had strong output in the areas of cancer, apnea and sleep related breathing disorders, tuberculosis, and pneumonia.[6] Our own group recently analyzed respiratory medicine research through publications in the journal *Archivos de Bronconeumología* and found that the areas of greatest activity were apnea and sleep related breathing disorders, and oncology.[4] A comparison between 3 decades (1970, 1980, and 1990) of the evolution of production in each subject area revealed that activity had increased in the areas of asthma, apnea and sleep related breathing disorders, tuberculosis, non-tuberculosis infections, oncology, circulation, the pleura, and interstitial diseases: those findings were similar to reports from other authors.[6]

The original articles published in *Archivos de Bronconeumología* during 2006, which have achieved a very high level of both scientific and editorial quality, confirm the importance and widespread impact of respiratory medicine research. Every year, the quality of the articles published in *Archivos* improves, increasing the journal's international impact factor.[5,7] In 2006, 59 original articles were published in the journal, and in this review we will discuss these contributions by topic.

Correspondence: Dr. J.I. de Granda Orive.
Cavanilles, 43, 7.º E.
28007 Madrid. España.
E-mail: igo01m@gmail.com

Manuscript received April 11, 2007. Accepted for publication April 25, 2007.

Chronic Obstructive Pulmonary Disease

Miravitlles et al[8] published a study with a dual objective: first, to assess the diagnostic attitude of primary care physicians towards hypothetical cases of patients of both sexes with COPD characterized by the same symptoms and degree of exposure to tobacco; and second, to investigate the influence of lung function test results on diagnosis. The authors' initial hypothesis was that physicians would be less likely to diagnose COPD in women. Interestingly, they found that men were more likely than women to be diagnosed with COPD on the basis of clinical presentation and the results of a physical examination, but that this gender bias disappeared when the physicians were given the results of spirometry. This study confirmed that men are more likely than women to be diagnosed with COPD on the basis of a medical history, smoking history, and the results of physical examination. Domingo et al[9] posed the question of whether a specialized hospital unit for patients with COPD and respiratory insufficiency would improve the effectiveness and efficiency of their care. Prospectively, they compared results for the study group with historical control data, analyzing clinical variables and quality of life in addition to a series of variables relating to health care and costs. One notable finding was that 13% of the patients were smokers. At the end of the follow-up period, significant improvements were found in forced vital capacity and PaO_2, while forced expiratory volume in 1 second (FEV_1) and $PaCO_2$ tended to improve, but not significantly. Overall quality of life, assessed using the Chronic Respiratory Questionnaire (a specific tool), also tended to improve, but not significantly. Dyspnea was the only domain in which the improvement was significant. A reduction was found over the study period in the number of emergency visits, hospital admissions, and inpatient bed-days. This led the authors to conclude that the proposed health care model slows down functional deterioration in these patients and reduces expenditure.

The efficacy of heparin in the prevention of venous thromboembolism in nonsurgical hospitalized patients is an interesting and controversial topic.[10,11] Modesto Alapont et al[12] conducted a prospective randomized trial in patients with severe COPD requiring domiciliary oxygen therapy. The patients were assigned upon discharge after hospitalization for a COPD exacerbation; the treatment group received daily low molecular weight heparin for 6

months and the control group did not. Two of the interesting findings in this study were that the prevalence of thromboembolic disease was not high among these patients with severe COPD and that prophylactic treatment with low molecular weight heparin had no positive affect on survival. Another noteworthy finding was the frequency of bleeding complications necessitating withdrawal of treatment. A limitation of this study noted by the authors was the small sample size, making necessary larger studies to confirm these results.

In a multicenter observational pharmacoeconomic study of a population of patients with controlled chronic bronchitis and COPD in a primary care setting, Llor et al,[13] aimed to identify the variables associated with higher health care costs on the basis of a pharmacoeconomic assessment. They found that the exacerbations associated with the highest cost occurred among older patients with a greater degree of baseline dyspnea and a lower mean FEV_1. Multivariate analysis with high cost as the dependent variable, revealed that the variables predictive of high cost were continuous home oxygen therapy and previous hospitalization.

To ascertain whether patients with COPD with the same level of airflow limitation but different clinical phenotypes have different degrees of pulmonary or systemic inflammation was the objective of a study by Izquierdo et al.[14] One of the most interesting results of this study was that the patients diagnosed with COPD had significantly higher neutrophil counts than the controls; in contrast, the differences in this variable between COPD phenotypes were not significant. Compared to the control group, serum concentrations of interleukin-8 were significantly higher in patients with emphysema, and fibrinogen levels were higher in the patients with chronic bronchitis. Once again, no significant differences were found between COPD phenotypes in these parameters. Serum levels of leukotriene B_4 were significantly lower in the emphysema group. Concentrations of interleukin 8 and 8-isoprostane in exhaled breath condensate were significantly lower in the patients with emphysema than in the group with chronic bronchitis and the controls. The pH of exhaled breath condensate samples was lower in the COPD patients than in the controls, but no difference was found between the 2 phenotypes. Interleukin 8, leukotriene B_4, and 8-isoprostane levels in exhaled breath condensate correlated significantly with the ratio of carbon monoxide diffusing capacity to alveolar volume, but not with FEV_1. In light of these findings, the authors concluded that emphysema is associated with a reduced degree of pulmonary inflammation and oxidative stress

The need for simple techniques to evaluate functional capacity in patients with COPD has given rise to the development of several tests, including the step test and the shuttle walk test with an external sound stimulus.[15,16] The objective of a study by Warken Rosa et al[17]was to optimize the application of the shuttle walk test by modifying the external sound stimulus in such a way that each beep corresponded to a step to help the patients adapt their pace more precisely to the required speed for each shuttle. The authors found that patients covered a greater distance in the walk test when this was accompanied by the modified sound stimulus that guided their pace. Likewise, it is also useful to know whether patients with COPD are less active than healthy individuals. To study this parameter, Lores et al[18] measured daily physical activity in COPD patients using a triaxial accelerometer during a conventional recording period and alternative periods, and analyzed the medium-term repeatability of these measurements. The authors found that COPD patients had a lower level of physical activity than the healthy volunteers. The results obtained with the accelerometer also showed good agreement between measurements during different recording periods in the same week and acceptable repeatability. Results obtained with the accelerometer correlated well with 6-minute walk distance, dyspnea, and degree of airway obstruction.

Obviously, the next question that arises is whether functional capacity and survival improve in patients with COPD who follow a pulmonary rehabilitation program. This was investigated in a study by López Varela and coworkers.[19] While it is well known that patients with COPD are exercise intolerant,[18] rehabilitation, now a component of the treatment regimens for these patients, reduces perception of dyspnea and improves exercise tolerance and peripheral muscle characteristics.[20] Following a program designed to increase the patients' and their families' knowledge of the disease and its management, and to teach patients how to use inhalers and control exacerbations and provide them with psychosocial and nutritional support as well as physical training, the authors compared the results for a series of parameters obtained before and after the intervention. They found significant improvement in FEV_1, dyspnea scores (Borg scale), and results for the cardiopulmonary exercise test and the 6-minute walk test. Improvement in quality of life (measured using the Spanish version of the St George's Respiratory Questionnaire) was statistically significant only in the symptoms subscale. The best predictors of survival were lung function at rest (the higher the FEV_1, the longer the survival), and the 6-minute walk distance (the greater the distance walked before pulmonary rehabilitation, the longer the survival). In contrast, no correlation was found between nutritional status and mortality, or between the BODE index (combining body mass index, airflow obstruction, dyspnea, and exercise capacity[21]) and survival. Based on these findings, the authors concluded that patients showed both clinical and functional improvement and achieved better exercise tolerance levels after the rehabilitation program, and that survival correlated with lung function and initial exercise capacity. Survival rates were lower (but not significantly) in patients with lower quality-of-life scores, higher BODE scores, and older age.

Soler et al[22] demonstrated that a program designed specifically for COPD patients with a history of frequent exacerbations incorporating basic educational support and regular clinical monitoring can substantially reduce the frequency of exacerbations, and thereby minimize both the number and duration of hospital stays. The reduction in the number of exacerbations was associated with significant clinical improvement as measured by the quality-of-life questionnaire. As in the study discussed above, this improvement was seen particularly in the symptoms domain. A reduction in the progressive loss of lung function was also observed.

The importance of COPD as a cause of mortality and disability, the prevalence of this disease in Spain,[23] and the enormous expense it entails make it essential to reduce the associated costs. One way to do this is through proper management during the initial stages of the disease. In this context, Naberan et al[24] designed a study to find out more about the situation regarding the diagnosis and treatment of COPD in primary care. They collected information using 2 questionnaires: the first on COPD treatment and the second on the use of spirometry to diagnose the disease. One of the noteworthy results of this investigation was that the primary care physicians correctly identified the presence of airflow obstruction, but failed to correctly classify patients in the different stages. The questions for which the lowest percentages of correct answers were obtained were those relating to the indications for bronchodilator treatment and arterial blood gas analysis and the correct use of the expiratory maneuver. The question with the highest rate of correct responses concerned the indications for spirometry, suggesting that the primary care clinicians correctly identified the group of at-risk patients.

Another very interesting study published in *Archivos* in 2006 dealt with the topic of spirometry in primary care.[25] Spirometers were available in almost all the primary health care centers in Navarre, the authors found, but very few tests were being performed and technical defects were common (spirometers calibrated irregularly or not at all). The authors also found a lack of specific training among the personnel responsible for performing spirometry. In short, a high percentage of the spirometries carried out failed to meet recommended reproducibility criteria, and significant differences were found between the means of forced vital capacity and FEV_1 obtained in the primary care setting and in the pneumology department. This imprecision gave rise to incorrect diagnoses and a tendency in primary care settings to falsely diagnose patterns as restrictive and incorrect classification of the severity of the obstruction.

Abreu González et al[26] were responsible for the only article published in 2006 dealing specifically with the treatment of COPD. They investigated whether intravenous magnesium sulfate had a bronchodilator effect in patients with COPD exacerbations and whether it would enhance the bronchodilator effect of β_2-agonists. They concluded that intravenous magnesium sulfate alone had no bronchodilator effect in patients with exacerbated COPD. However, a significant increase in FEV_1 (both absolute and expressed as a percentage) was observed after administration of inhaled salbutamol in the group that received magnesium sulfate.

The systemic effects of COPD that have been most studied are the loss of muscle mass and the dysfunction associated with such loss; these aspects are also of prognostic interest in this disease.[27] Martínez Llorens et al[28] undertook a study to assess weakness or fatigue of the diaphragm and to compare the results obtained using 2 different techniques: forced inhalation from residual functional capacity or residual volume, the maneuver from which transdiaphragmatic pressure at maximum effort (Pdisniff) is determined, and cervical magnetic stimulation to obtain a contractile response from the diaphragm. They concluded that cervical magnetic stimulation is a good alternative to voluntary maneuvers in clinical practice. The main advantage is its high sensitivity, but this is achieved at the expense of a high rate of false positives for muscle weakness. This technique is particularly useful for ruling out diaphragmatic dysfunction in patients who have comprehension difficulties or are in a critical situation.

Sleep-Related Respiratory Disorders

In order to investigate the relationship between sleep-disordered breathing and difficult-to-control hypertension, Martínez García et al[29] designed a study that enrolled all the patients treated in their hospital with suspected difficult-to-control hypertension. Daytime and nighttime systolic blood pressure was found to be significantly more uncontrolled in the patients who had a higher incidence of sleep-disordered breathing events, and these patients also required a larger number of drugs. Blood pressure results were also worse in patients with severe sleep apnea-hypopnea syndrome (SAHS) than in patients with mild forms of this syndrome. In the patients with SAHS, a significant relationship was also observed between systolic and diastolic blood pressures and both the body mass and apnea–hypopnea indices; multivariate analysis confirmed both indexes to be predictors of hypertension.

While obesity is a known predisposing factor for SAHS, this association is not so clear in children. In a consecutive sample of children referred to a pediatric respiratory medicine outpatient clinic for suspected sleep apnea and/or snoring, Sardón et al[30] analyzed the possible association between obesity and SAHS among those diagnosed with the latter. The prevalence of SAHS was 74.5% in the sample of 400 children studied. Obesity was found to be independent of age and not associated with SAHS, number of snores, or mean and minimum oxygen saturation in arterial blood. Obesity is known to be associated with various diseases including those that form part of the so-called metabolic syndrome, such as type 2 diabetes mellitus and lipid metabolic disorder, and also with elevated plasma concentrations of uric acid and a higher frequency of episodes of gout. It also increases the risk of cardiovascular disease and is linked to a higher incidence of respiratory disease, in particular SAHS. Ruiz García et al[31] designed a study to analyze the relationship between uric acid levels and sleep-disordered breathing. They found a significant positive correlation between uric acid levels and the number of apneas and hypopneas, the number of desaturations, and the cumulative percentage of time with oxygen saturation under 90%, body mass index, waist-to-hip ratio, diastolic blood pressure, and triglyceride and cholesterol levels. Conversely, they found a negative correlation between uric acid levels and initial arterial oxygen saturation in the sleep studies and PaO_2. In that study, uric acid levels were higher in the patients with severe SAHS. However, as this difference disappeared when the influence of confounding factors was considered, uric acid level is not useful as a biological marker.

Hernández et al[32] investigated whether treatment with nasal continuous positive airway pressure (CPAP) reduces

oxidative stress in patients with SAHS. They used circulating malondialdehyde as the marker of oxidative stress. Diagnosis was confirmed by polysomnography and all participants underwent nasal CPAP titration. On follow-up 3 months after diagnosis, patients were reassessed, objective adherence was checked by taking the time counter reading, and a second blood sample was taken to quantify malondialdehyde levels. Controlling for hyperc holesterolemia, smoking, and diabetes, the authors observed significant differences in mean plasma concentrations of malondialdehyde before and after treatment. In the controls, on the other hand, initial malondialdehyde concentrations were lower than in the patients with SAHS, and that difference did not change at the end of the study period. Consequently these authors concluded that oxidative stress decreased significantly in the group of patients with SAHS treated with nasal CPAP.

Respiratory Insufficiency

Starting from the hypothesis that patients who have not previously suffered an episode of bronchospasm would be less likely to recognize induced bronchospasm than those who have experience of such an event, Martínez Moragón et al[33] compared differences in perception of dyspnea between a group of patients with intermittent asthma and a group who had no lung disease and had never experienced acute airway obstruction. They found that for the same degree of obstruction, and for all the degrees of obstruction analyzed during the bronchial challenge test, the degree of dyspnea perceived by the inexperienced individuals was notably lower than that perceived by the experienced ones. These findings support the hypothesis that appropriate perception of dyspnea in this context is based on prior experience. As a result of the prior observation that a subgroup of patients had an exaggerated perception of breathlessness during acute bronchoconstriction, the same research team investigated the question of whether such over-perception was sporadic or stable over time, and whether an association existed between over-perception of dyspnea and hyperventilation syndrome.[34] A group of asthmatic over-perceivers was followed for 10 years. They continued to be over-perceivers although the severity of their asthma did not change appreciably. However, by the end of the follow-up period, these patients did perceive their asthma to be less severe and reported lower levels of dyspnea at rest; they also had fewer exacerbations and a lower level of anxiety. These findings answer the first question by confirming that over-perceivers tend to remain so over the years. With respect to the second question, no association was found between hyperventilation syndrome and over-perception.

Another interesting topic related to dyspnea is the vocabulary used to describe breathlessness in Spanish, and more specifically in the Spanish spoken in Mexico. Vázquez García et al[35] designed a study to identify the terms used to describe shortness of breath and their association with various diseases. They also studied healthy individuals who experienced dyspnea in physiological states, such as exercise and pregnancy. They found 21 descriptors, which were classified using cluster analysis into 7 groups that may reflect different sensations or types of dyspnea. For most of these terms, reproducibility and agreement were acceptable. Healthy individuals in respiratory distress and patients with cardiovascular or pulmonary disease tended to use terms from certain clusters more often.

In a prospective study of hypoxemic patients with COPD, congestive heart failure, or obesity-hypoventilation syndrome who had hypercapnic acidosis, Ortega González et al[36] assessed initial state, response to conventional initial treatment, and study outcomes (in terms of both clinical course and blood gases) after the start of noninvasive ventilation in order to determine the prognosis of the disease and evaluate the protocol. With conventional treatment, an improvement was observed in PaO_2, but hypercapnia got worse and pH remained abnormal in all 3 groups. In contrast, once noninvasive ventilation was started, an improvement was observed for all 3 groups in pH (significant in the COPD group and among the patients with obesity-hypoventilation syndrome), PaO_2 (only significant in the COPD group), and $PaCO_2$ (significant in the group with obesity-hypoventilation syndrome). Moreover, during the first 12 to 24 hours of ventilation, pH values returned to normal in the COPD and obesity-hypoventilation syndrome groups. Based on these findings, the authors concluded that noninvasive ventilation is more effective in patients with obesity-hypoventilation syndrome and COPD (with similar initial severity as reflected by arterial blood parameters). They also noted that initial conventional treatment does not reverse acidosis, and that patients with COPD have the poorest response to conventional treatment; hence the need to start noninvasive ventilation promptly.

Following on from that study, Bertrand et al[37] developed a program of home ventilatory assistance for children with chronic respiratory failure who were followed by their hospital service. Their objective was to characterize the population of children on home ventilatory assistance by diagnosis and type of support in order to provide information for the creation of a national program. The reasons for assisted ventilation were neuromuscular disease, airway disease, cardiopulmonary disease, and hypoventilation syndrome. Invasive ventilation via tracheostomy was necessary in 26 of the 35 children (16 of whom were on CPAP and 10 were, on synchronized intermittent mandatory ventilation). In the other 9 children, ventilation was delivered through a nasal or an oral–nasal mask (bilevel positive airway pressure in 8 and CPAP in 1). The authors concluded that the home ventilatory assistance program was safe and necessary, and that the professional support provided in the home to these children had a positive effect on outcomes. However, they also commented that technical coordination needs to be improved and minimum specifications established if equipment-related problems are to be prevented. In order to provide useful tools for monitoring domiciliary mechanical ventilation, López Campos et al[38] produced a translation of the Severe Respiratory Insufficiency (SRI) questionnaire that was culturally adapted for the Spanish population. The SRI is a multidimensional health-related

quality-of-life questionnaire specifically designed for patients receiving home mechanical ventilation.

Bronchiectasis

Bronchiectasis remains an important cause of morbidity and mortality. In this context, Yuncu et al[39] retrospectively evaluated the outcomes of surgical treatment in a group of patients with this condition and as might be expected, they found the functional results of surgical treatment to be positive and promising, particularly in carefully selected patients who had localized disease. In those patients, outcomes after complete resection were better.

Pathophysiology and Functional Assessment

It is known that during incremental exercise a transition occurs from respiration in which ventilation increases largely at the expense of tidal volume to tachypneic respiration. In other words, above a given intensity, tidal volume reaches a stable value or increases only slightly, and past this point breathing rate contributes more to the increase in expiratory volume. There is still some debate about the role of the Hering–Breuer reflex in the control of ventilation during exercise in humans, although it has been shown to play a role in animal models. Benito et al[40] analyzed breathing pattern response to ascertain indirectly whether the Hering–Breuer reflex is activated and whether it participates in the control of breathing. They found that the inspiratory off-switch threshold correlated directly with the ratio of tidal volume to inspiratory time and with the second ventilatory threshold (the load at which oxygen uptake is no longer proportional to carbon dioxide production) and suggested that the reflex may participate in the control of the breathing pattern during exercise. This finding may have application in patients with COPD.

In another interesting study, Herrejón et al[41] analyzed the agreement, accuracy, and correlation of transcutaneous carbon dioxide pressure ($TcPCO_2$) with $PaCO_2$ when monitoring arterial blood gas parameters in patients hospitalized for pulmonary disease. They showed $TcPCO_2$ and transcutaneous oxygen saturation (measured using the same device) to be useful parameters for monitoring clinical course in patients with respiratory disease without the need for repeated arterial punctures. Some limitations were cited, including greater dispersion in extreme $TcPCO_2$ values and a slight variation in transcutaneous oxygen saturation.

In an international multicenter study of a large sample of patients, Pérez Padilla and colleagues[42] analyzed reference values for spirometry in 5 cities in Latin America. The proposed reference values represent an improvement over those currently available, and this advance will contribute to better use of spirometry in Latin America.

Asthma

To find out whether the incidence of near-fatal asthma is decreasing in Spain, Bellido Casado et al[43] designed a retrospective observational study to evaluate changes in the annual incidence of near-fatal asthma in recent years in several Spanish hospitals. They found that the number of cases of near-fatal asthma had decreased gradually over the period analyzed, indicating that the incidence of near-fatal asthma is, in fact, decreasing in Spain.

Of equal interest to this investigation of the evolution of prevalence over the years is another study that focused on a possible technique for detecting asthma. Oñate et al[44] evaluated the usefulness of the shuttle-run, a physical fitness test used in school physical education programs, as a way of detecting asthma. They conducted a cross-sectional observational study of school children between the ages of 6 and 12 years based on the asthma symptom questionnaire and 2 physical fitness tests (a shuttle run test and a free running test at maximum effort) using peak expiratory flow as the main outcome measure. They found no association between the 2 physical fitness tests and concluded that the shuttle run is not a valid test for the detection of suspected asthma.

The burden of asthma-related care on the public health system is well known. Although we now have effective tools to treat this disease, we still need more information about patients' satisfaction with their treatment. For this reason, international guidelines suggest that, in addition to improving patients' understanding of asthma and its management, we must also improve their satisfaction and thereby increase their confidence and compliance with therapy and improve self-management. As there is currently no instrument validated for the Spanish population for measuring satisfaction in patients with asthma, Martín Fernández et al[45] designed a study to assess the psychometric properties and feasibility of the Spanish adaptation of the Satisfaction With Inhaled Asthma Treatment Questionnaire (SATQ). They found that the SATQ is easy for patients to complete and has acceptable validity and reliability. The Spanish version has a domain structure that is similar but not identical to the English version. Despite this difference, they recommend the SATQ as a good instrument for evaluating the satisfaction of asthmatic patients with their inhaled treatment.

Recent decades have seen an increase in the prevalence of asthma in adolescents, but no satisfactory explanation has been found for this development. Asthma has been associated with environmental, behavioral, and genetic factors, but many of the findings are conflicting. Consequently, more research is necessary to determine the association between family history of allergy, smoking, obesity, and asthma. This was the objective of a study by Vázquez Nava et al,[46] who found that a higher percentage of asthmatic adolescents reported living with smokers or having parents who had allergic asthma or rhinitis. The effect of the presence of smokers in the home on the prevalence of asthma among adolescents was significant. Obesity was found to have some effect on asthma, but no relationship was found with active smoking. More of the adolescents with symptomatic asthma had a family history of allergy and passive smoking, but no association was found between having symptoms and active smoking or obesity. Based on their findings, the authors concluded that a family history of allergy was the most important risk factor for onset of asthma or asthma symptoms, and

that the risk of developing the disease increased with obesity and involuntary exposure to tobacco smoke.

Smoking Addiction

Smoking addiction is a subject that generates a great deal of research activity with an acceptable impact,[47] and *Archivos de Bronconeumología* is a one of the journals in which studies in this multidisciplinary field are frequently published. Smoking among adolescents and the factors that influence young people to start smoking is a recurring theme. Yáñez et al[48] designed a study to determine the prevalence of smoking among adolescents, and to analyze the association between smoking and the home and school environment. One notable result they reported was that bivariate analysis identified the following factors to be significantly associated with smoking: older age, rural as opposed to urban residence, attendance at a public rather than a private school, living with only 1 parent, and eating meals alone. The results of multivariate analysis were similar; smoking was found to be significantly and independently associated with public schooling, urban residence, single-parent family, having lunch at school, and eating alone.

An association has been found between COPD and several collagenases (particularly matrix-metalloproteinases [MMPs] 9, 1, and 2) that regulate the homeostasis of the pulmonary matrix, which is composed of collagen and other proteins. Their usefulness as markers of remodeling has been reported, specifically the overproduction of MMP-9 and an imbalance between this proteinase and its inhibitor, the tissue inhibitor of metalloproteinase (TIMP) 1, in COPD.[49] In an interesting cross-sectional observational study, Avilés et al[50] assessed the equilibrium between MMP-9 and TIMP-1 in induced sputum from healthy smokers and healthy nonsmokers. A third group of subjects with COPD was included as a reference. They found that patients with COPD had signficantly higher levels of MMP-9 than the healthy smokers or the control nonsmokers. MMP-9 levels also tended to be higher in the healthy smokers than the nonsmokers, but this difference was not significant except in the group of participants with a smoking history of 20 pack-years or more when the results were analyzed by cigarette consumption. TIMP-1 levels declined progressively from healthy subjects to patients with COPD. The patients with COPD had the highest ratio of MMP-9 to TIMP-1, higher than smokers who did not have COPD (who had an intermediate ratio) and healthy subjects. Perhaps the most interesting finding in this study was a significant inverse correlation in all groups between the ratio of MMP-9 to TIMP-1 and FEV_1; this correlation was stronger in the COPD group. This finding may indicate that the increased presence of enzymes in the airway plays a role in the histologic changes seen in smokers.

Oncology

In a national prospective multicenter study assessing clinical and epidemiological variables, Sánchez de Cos Escuín and coworkers[51] studied the hospital incidence of lung cancer by collecting clinical and therapeutic data in addition to information on how the disease was managed. The standardized incidence rates ranged from 42.4 to 63.2 per 100 000 population in men, and from 2.5 to 23.4 per 100 000 population in women, with a higher proportion of men overall (a ratio of men to women of 8.5:1) and a mean age of 67 years in both sexes. In total, 97.5% of men and 32% of women were smokers or ex-smokers. Analysis of histologic diagnosis revealed a clear predominance of non-small cell cancer (NSCLC), and diagnosis was established in the more advanced TNM stages in these cases. The predominant treatment regimen was, therefore, chemotherapy and/or radiotherapy (55.4%). The most noteworthy results of this study were the increase in the percentage of lung cancers in the period studied as compared to the period 1990-1999, the overall increase in the proportion of women with this disease, and the very high number of pack-years reported in both smokers and ex-smokers.

As we have noted in relation to the study above,[51] the most common histological type of lung cancer in Spain was NSCLC, a group that includes the subtype bronchioloalveolar carcinoma (BAC). López Encuentra et al[52] described a series of cases of BAC treated surgically between 1993 and 1997 in the 19 hospitals that participate in the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). In 82 patients (3%) there was evidence of BAC in excised tissue, more women were diagnosed than men, and diagnosis was more often the result of a chance finding in women. Patients with BAC reported very slight or no dyspnea, and a comparison between this group and the patients with other types of NSCLC revealed significant differences in general clinical status, weight loss (less marked in patients with BAC), presence of comorbidities in general, and of COPD in particular (less common in BAC). Significant differences were also found in smoking status (greater proportion of nonsmokers), tumor size, and hematologic parameters. BAC was found more often than other types of NSCLC as stage cI (in 12% more cases) and stage pI (22% more). Complete resection was more likely in BAC, and the rate of survival at 5-years was higher.

Cayuela et al[53] analyzed the evolution of mortality from lung cancer in Andalusia between 1975 and 2002. They found a reduction in mortality related to lung cancer that correlated with the decrease in the prevalence of smoking during the same period. However, mortality increased among young women. Apart from knowing the evolution over time of lung cancer mortality rates, we also need data on hospital expenditure related to the diagnosis of cancer. In order to obtain such data, Abal Arca et al[54] analyzed the direct cost of lung cancer diagnosis in 2003 and found that the mean cost per patient diagnosed in an outpatient clinic was 62% lower than the expenditure associated with hospital admission for diagnosis. The mean cost of diagnosing NSCLC was higher than that of small cell carcinomas, and diagnosis was more costly in more advanced stages than in the early stages of disease.

Fiberoptic bronchoscopy is the procedure most often used to diagnose lung cancer. To improve the yield of

bronchoscopic diagnostic techniques, Fernández Villar et al[55] investigated whether the order in which bronchial washing is performed relative to bronchial brushing and forceps biopsy had any effect on diagnostic yield. They found that the combined yield of washing before and after brushing or biopsy was significantly higher than either washing before or after the other sampling techniques. In any case, the order in which bronchial washing is performed with respect to the other techniques did not appear to influence diagnostic yield.

Gullón Blanco and colleagues[56] investigated the prognostic factors that might be related to survival in patients with advanced NSCLC, and whether cytostatic treatment was an independent predictor. They showed that chemotherapy in normal clinical practice significantly prolonged survival in patients with a performance status of less than 2 on the Eastern Cooperative Oncology Group scale, and that this increase is greater if there is no associated weight loss. Jímenez et al[57] compared survival, morbidity, and mortality rates for a series of patients who underwent either bronchoplastic sleeve lobectomy or pneumonectomy to treat NSCLC. They found pneumonectomy to be associated with a higher perioperative mortality (9.1% vs 2.8% in the lobectomy group) and a lower overall survival rate (32% vs 56%). When the data were stratified by node involvement, the 5-year survival rate for patients at pathological stage N0-N1 in the lobectomy group remained higher (60% as compared to 39% in the pneumonectomy group). These results led the authors to conclude that sleeve lobectomy offers better survival than pneumonectomy for patients with N0-N1 NSCLC.

In a study of new treatment options for lung cancer, Rodrigo Garzón and colleagues[58] used an animal model to investigate the possibilities of gene therapy—using genetic material, both genes and vectors, for therapeutic purposes. These authors concluded that the 3 treatments used—replication-defective recombinant adenovirus carrying the gene for thymidine kinase or interleukin-12, and syngeneic dendritic cells previously transduced with adenovirus containing the IL-12 gene—were all effective. In the animal model, they led to a reduction in subcutaneous tumor growth as compared to the control group.

Tuberculosis and Respiratory Infections

Tuberculosis

In a descriptive study, Bran et al[59] analyzed the characteristics of the outbreaks of tuberculosis studied by the Catalan epidemiological surveillance department during the period 1998-2002. They analyzed 27 outbreaks (defined as 3 or more associated cases in one year), 70% of which occurred in family environments, with a mean annual incidence of 0.40 outbreaks per 100 000 population. The authors of that study found a trend towards increasing incidence over the study period, a predominance of cavitating pulmonary tuberculosis, and higher prevalence among men (62%) and in the cohort between 16 and 49 years of age. Only 2 index cases were infected by human immunodeficiency virus, and none were immigrants. Another important finding was that a longer diagnostic delay (which ranged between 31 and 71 days) was associated with a higher number of secondary cases.

Nontuberculous Infections

Initial treatment of community-acquired pneumonia (CAP) must be empiric, and the choice of therapy is an important prognostic factor. Among the causes of CAP are the so-called atypical pathogens, although there is still some debate about the real incidence and clinical importance of these microorganisms. In a prospective study of 390 patients diagnosed consecutively with CAP and requiring hospitalization, in which strict serological analysis was used for the etiologic diagnosis, Fernández Álvarez and coworkers[60] found that 89 cases were caused by atypical pathogens. The patients with CAP caused by atypical pathogens were then assigned to 2 groups according to whether or not the antibiotic treatment they received provided coverage. The authors found that antibiotic therapy giving specifically covering atypical pathogens did not improve clinical course or radiographic resolution in these patients.

Capelastegui et al[61] used internationally accepted quality indicators in a 4-year study monitoring changes in the quality of treatment provided after the implementation of a practice guideline for the management of patients diagnosed with CAP in the emergency department. The guidelines gave evidence-based specifications for the care all patients would receive for CAP. Compliance was monitored using a series of predefined indicators. As a result of the guidelines implemented, there was an improvement in quality-of-treatment indicators over the 4-year study, and a reduction in the number of both admissions and length of hospital stay. Systematic monitoring of a series of indicators related to guidelines for practice provided insight and allowed these physicians to evaluate their clinical practice, a strategy that led to improved outcomes.

Due to the paucity of studies on the prevalence of the different pathogens that cause chronic bronchitis in the community, Llor et al[62] designed a study to investigate this question in a primary care setting. This was an observational cross-sectional multicenter trial that enrolled 1947 patients with mild-to-moderate exacerbations. Of the 1537 sputum samples collected, 498 had good cell quality for microscopic examination. The pathogens most commonly isolated were *Streptococcus pneumoniae* (34.8%), *Moraxella catarrhalis* (23.9%), and *Haemophilus influenzae* (12.6%). Amoxicillin resistance was found in 1.2% of the isolates, and macrolide resistance in 34.5%.

Based on the premise that a pulmonary infection should be accompanied by changes in the redox state at the airway surface and be characterized by an increase in the concentration of oxidants in exhaled breath condensate, Romero et al[63] found that an analysis of this parameter facilitated the detection of oxidative stress at the airway surface in patients with severe lung infections. Oxidative stress was assessed by measuring the concentration of 8-isoprostane (an index of lipid peroxidation in vivo) and myeloperoxidase (an indicator of the intensity of both the

neutrophil reaction and oxidative activity) in exhaled breath condensate samples.

Circulation

In recent years, a number of new drugs have been incorporated into the meager repertory of medications for the treatment of pulmonary arterial hypertension. These include the endothelin receptor antagonists, and in particular bosentan. Román et al[64] published an article describing their work with bosentan in the long-term treatment (mean follow-up of 15.7 months) of patients with functional class III pulmonary arterial hypertension. They concluded that long-term treatment with this drug in a real clinical situation improved or stabilized exercise capacity in 2 out of every 3 patients.

In recent years, computed tomography (CT) of the chest has replaced ventilation–perfusion scintigraphy in the diagnosis of pulmonary embolism. However, significant variations have been found in the sensitivity (53%-100%) and specificity (73%-100%) of this technique, making additional diagnostic tests necessary in the case of a negative result. In a retrospective study, Jiménez et al[65] analyzed the yield of chest CT-angiography in ruling out a diagnosis of pulmonary embolism and ascertained the percentage of patients with a negative CT angiogram for whom an additional test was ordered. The CT-angiogram was positive—that is, diagnostic of pulmonary embolism—in 38% of patients (60 out of 159). However, a thromboembolic event was later diagnosed in 35 of the 99 patients whose CT-angiogram had been negative (a sensitivity of 63% and a negative predictive value of 65%), a result indicative of a 35% risk of developing pulmonary embolism in the 3 months following a negative CT angiogram. CT-angiography provided an alternative diagnosis in 13 out of 65 patients. Another interesting finding in this study was the high clinical probability associated with a significantly higher risk of another thromboembolic event within 3 months of the CT scan. The risk of such an event was significantly reduced when an alternative diagnosis was established by the CT. Based on these findings, the authors concluded that single-detector row helical chest CT-angiography should not be used as the sole test to rule out pulmonary embolism.

Diagnostic Techniques

De Gregorio et al[66] published their work on the endovascular treatment of massive hemoptysis by bronchial artery embolization after a 15-year follow-up. Clinical success was the outcome in 91.1% of patients with massive hemoptysis who underwent embolization of the diseased arteries. A second embolization was required in 6.7% and was effective in 52.6% of these cases. Thoracotomy was required in 6 patients. Over the next 15 years, 28.4% patients were lost to follow-up for various reasons, 22.3% had a recurrence of hemoptysis on 1 or more occasions, but repeat embolization was required in only 10.4% of these cases. The results of this study would suggest that embolization of the bronchial arteries is a safe and effective treatment in patients with massive hemoptysis.

In a retrospective, observational, and descriptive study, Mora et al[67] contributed their experience with the endoscopic treatment of bronchopleural fistulas. The endoscopic technique used was the instillation of sealing substances—Histoacryl (Braun Medical SA, Tuttlingen, Germany) and/or Tissucol (Baxter SL, Vienna, Austria)—through a fiberoptic bronchoscope. The sealing substances closed the fistula in 85.7% of the patients with no associated complications, and fewer than 3 applications were required in 85.7%. This result indicates that the technique makes surgery unnecessary, achieves closure of the fistula in a high percentage of cases with a low number of applications and no morbidity.

Resource Management

Appropriate use of hospital resources is important because of the high cost of hospital care. It is, therefore, crucial to gather information on the appropriateness of hospital admissions and stays. Careful monitoring of the situation will ensure a higher quality of health care and better management of the available resources. Campos Rodríguez et al[68] analyzed the rate of inappropriate admissions over a 1-year period to a pulmonology department and established the reasons for such admissions. They classified 7.9% of the admissions as inappropriate, in 70% on the basis that the patients in question could have been treated as outpatients. The variables independently associated with inappropriate admissions were nonurgent admission and a tumor diagnosis as the reason for admission. In the context of optimizing resources and resource use, it is also useful to have data on the change over time in the profiles of the patients who attend a pneumology clinic. In a study analyzing the quantitative and qualitative changes in health care demand in a regional pneumology clinic over a 10-year period, Pellicer Ciscar[69] found the main changes to be a decline in the number of referrals from primary care clinics and emergency departments, and an increase in referrals from other sources They also found increases in obstructive sleep apnea syndrome (which became the most common reason for consultation) and right heart disease, and a decrease in tuberculosis cases.

Benchmarking, a continuous process designed to compare efficiency in terms of productivity, quality and working practices, is also of great interest in the context of health care management. Varela et al[70] applied the technique of benchmarking to the treatment of lung resection in 9 Spanish hospitals in order to identify areas for improvement in the execution of this surgical procedure. On the basis of the results they recommended systematic admission of patients undergoing lung resection, scheduling of presurgery and preanesthesia visits on the same day, and implementing practice guidelines for preoperative assessment by the anesthesiologist. When a surgical procedure is canceled the affected patient should be discharged and the procedure rescheduled for the earliest possible date. Patients referred from other departments should be discharged and subsequently readmitted. Postoperative analgesic protocols should be put in place, and patients should be discharged from hospital with

Heimlich valves as both of these measures influence the number of inpatient bed-days.

Pleural and Interstitial Disease

In a retrospective study, Gómez Caro et al[71] described and assessed the effectiveness and complications of video-assisted thoracic surgery for primary spontaneous pneumothorax. They concluded that video-assisted thoracic surgery with resection of pleural lesions and pleural abrasion is an effective and simple treatment for primary spontaneous pneumothorax irrespective of intraoperative findings.

Molina Molina and colleagues[72] hypothesized that the elevated expression of the gene that encodes transforming growth factor β_1 (TGF-β_1) in the lung tissue of patients with idiopathic pulmonary fibrosis would give rise to a corresponding increase in levels of circulating TGF-β_1, and they undertook a study to investigate the prognostic value of quantifying these levels in plasma. They concluded that the measurement of TGF-β_1 in plasma could be used in conjunction with other analytical data to diagnose idiopathic pulmonary fibrosis, but not as a biomarker because the parameter was not shown to be useful for predicting either disease prognosis or response to treatment.

Miscellaneous

Four original articles can be assigned to the category of miscellaneous studies. Gómez Caro et al[73] determined the risk factors for atrial fibrillation after lung resection. These authors identified the following risk factors for atrial fibrillation: age 70 years or older, prior heart disease, lung cancer surgery, and type of lung resection (right bilateral lobectomy and left pneumonectomy). They concluded that development of atrial fibrillation after anatomical lung resection is a common complication associated with advanced age, a history of heart disease, prior lung cancer surgery, left pneumonectomy, and right bilateral lobectomy. In contrast, no association was found with hypertension, COPD, lung cancer stage, systematic lymph node dissection, or other forms of lung resection.

When a scientific association publishes guidelines on a specific disease or condition, the organization hopes they will be effective in daily clinical practice. In a prospective descriptive study carried out in a single public health district, Plaza et al[75] evaluated the usefulness of the SEPAR guidelines on the diagnosis and treatment of chronic cough.[74] Their assessment was based on the guidelines' ability to identify the possible causes of chronic cough, and they also reported the most common causes they found. Using the SEPAR guidelines, the authors were able to determine the cause of cough in 98% of patients, 91% using only stage I of the algorithm. In the majority of patients, cough was due to a single cause (53%). The most common causes were postnasal drip (46%), cough-inducing drugs (28%), asthma (27%), infection (23%), gastroesophageal reflux (21%), and other causes (16%). The SEPAR guidelines on chronic cough were effective in identifying the causes.

Freitas Fregonezi and colleagues[76] studied lung function abnormalities and health-related quality of life in patients with myasthenia gravis, and analyzed the relationship between these 2 sets of variables. Functional assessment of these patients revealed a slight restrictive pattern and a reduction in inspiratory muscle strength. Physical activity and the patients' general perception of their health were the health-related quality-of-life domains most affected.

Thoracic sympatholysis and sympathectomy are currently standard treatments for primary hyperhidrosis. Moya et al,[77] who assessed perioperative and postoperative complications in 520 patients following these surgical procedures, found that no deaths occurred and anhidrosis of the target area was achieved in 97.6% of the patients. Compensatory hyperhidrosis occurred in 48.4% of those operated and hypohidrosis in 2.2%. In 0.2%, the initial procedure was a failure and a second intervention was necessary. Mean length of stay in hospital was lower after sympatholysis. In 0.2% of cases, major intraoperative complications made conversion to thoracotomy necessary. The rate of postoperative complications was 5.2% (22.5% in sympathectomy and 3.5% in sympatholysis). The authors concluded that both of these surgical procedures are appropriate for the treatment of hyperhidrosis, but they recommended sympatholysis as the first line treatment because it is a simpler and less aggressive intervention.

In this review of the articles published in *Archivos de Bronconeumología* in 2006, certain articles merit special attention because of their great interest despite the fact that they are not original articles. One set of such articles comprises the SEPAR guidelines on the diagnosis and treatment of pleural effusion,[78] on occupational asthma,[79] and on the diagnosis and treatment of α_1-antitrypsin deficiency.[80] A review article on nicotine replacement therapy in pregnancy was also of great interest because of its social and health care implications.[81] Also important was the special article on SEPAR's position as a scientific association on the provision of tobacco cessation care and services in Spain.[82] From the clinical standpoint, we must make mention of the review articles on the following subjects: the affect of helminths on the respiratory system,[83] α_1-antitrypsin deficiency and the situation regarding this disease in Spain,[84] assessing the risk of bronchial asthma in children,[85] the situation regarding lung cancer in Spain,[86] and the relationship between rhinosinusitis and bronchiectasis.[87] The most important reviews relating to treatment dealt with the development of a new vaccine against tuberculosis infection,[88] the controversies regarding the treatment of extrapulmonary tuberculosis,[89] the use of anti-immunoglobulin E in the treatment of respiratory disease,[90] and the use of inhaled corticosteroids in asthma crises.[91]

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