HISTORICAL REVIEW

One hundred years of chronic obstructive pulmonary disease (COPD)

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Summary

Chronic obstructive pulmonary disease (COPD) is an increasing health problem and one of the leading causes of morbidity and mortality worldwide, but knowledge about its pathogenesis has increased substantially in recent years. The disease results from interaction between individual risk factors (like enzymatic deficiencies) and environmental exposures to noxious agents, like cigarette smoking, occupational dusts, air pollution and infections in childhood. The main mechanisms that may contribute to airflow limitation in COPD are fixed narrowing of small airways, emphysema and luminal obstruction with mucus secretions. COPD is characterised by a chronic inflammatory process in the pulmonary tissue, with a pattern different from bronchial asthma, associated with extrapulmonary effects and is considered now a complex, systemic disease. Optimal therapeutic targeting of COPD depends on a clear understanding of the precise mechanisms of these complex processes and on early and correct evaluation of disease severity. A combination of pharmacological and non-pharmacological approaches is used to treat COPD. Bronchodilators are the mainstay of COPD treatment and can be combined with inhaled corticosteroids for greater efficacy and fewer side effects. The use of LTOT for hypoxemic patients has resulted in increased survival, and expanded drug therapy options have effectively improved dyspnoea and quality of life. Recent studies have documented the benefits of pulmonary rehabilitation. In addition, non-invasive mechanical ventilation offers new alternatives for patients with acute or chronic failure.

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Epidemiology and risk factors of chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a relatively new term for an old disease. Terms such as “bronchitis”, “emphysema”, “asthmatic bronchitis” and “chronic bronchitis” were more commonly used in the past to describe
what we currently define as COPD. This review will highlight important papers published on the topic over the last 100 years in Respiratory Medicine and its previous versions British Journal of Tuberculosis, British Journal of Tuberculosis and Diseases of Chest and British Journal of Diseases of Chest.

Several publications have addressed the risk factors of COPD in the general population although early ones included only cohorts of working men with limited income. 

Rimington analysed data from mass radiography units and concluded that patients with chronic bronchitis were more likely to be old, heavy smokers and belong to a low social class. The mean age-adjusted prevalence rate for chronic bronchitis in that cohort was 12.3% in all men and 5.6% in all women. However, this was highest in patients who smoked 20 or more cigarettes per day (20% and 18.5% in men and women, respectively). In a subsequent publication, the same author demonstrated that the prevalence of chronic bronchitis in individuals who inhaled while smoking was 50% higher than in those who did not. It is unclear why only a minority of smokers develop a clinically significant disease. In addition to smoking, genetic risk factors such as alpha1-antitrypsin deficiency play an important role in some patients.

The impact of COPD

COPD is associated with significant morbidity and mortality worldwide and is currently a global health priority. In 1954, a study by Stuart-Harris evaluated the epidemiology and evolution of chronic bronchitis and described morbidity data collected from practitioners’ visits, industrial records and National Insurance data. These data revealed that in 1950, “bronchitis” was the second leading cause of incapacity from sickness and the sixth most common cause of claims of sickness in both men and women in Great Britain. Bronchitis, as a cause of sickness, was scattered over the whole ages in women but was more common in old men than young men. However, the author admits that there was no way to differentiate acute bronchitis from chronic bronchitis from that database. The same paper evaluated another field survey of patients with bronchitis and described a group of symptomatic patients with a “triple complex” syndrome of cough, sputum and disability (dyspnea or history of exacerbation). Patients with this “triple complex” were more likely to be old and had a high incidence of hospitalization. This was one of the few papers published at that time which attempted to classify the severity of COPD. In a subsequent paper published in 1964, the formation of a bronchitis registry in East London was described and patients were divided into three groups (Group 0, 1 and 2) according to severity of symptoms and lung function abnormality. The authors further analysed the characteristics and the impact of the disease in these groups demonstrating that patients belonging to Group 2 had the highest morbidity and had more time lost from work than patients in the other two groups. The burden of COPD in different countries was a focus of several publications over the last 100 years. In a report published in 1960 from the East London cohort, Caplin and Silver reported that unemployment and time lost from work were significant in patients with chronic bronchitis. The authors concluded that “the chronic bronchitic suffers from two disabilities which may make it difficult for him to retain his usual employment or find a new employment. These are increasing shortness of breath on exertion and lung infections which force him to be away from work …”. It is of great interest that almost 50 years later, the same problems are major causes of disability in patients with COPD. Utilization of healthcare services and hospitalizations driven by disease severity account for a major component of the total cost of COPD worldwide. The confronting COPD in North America and Europe survey which was the first large-scale international survey of the burden of COPD estimated the annual cost of healthcare utilization in the US at $4119 per patient with COPD, with indirect cost of $1527 per patient. The annual estimated societal cost was $5646 per patient. Inpatient hospitalization accounted for the majority of this cost ($2891). The same survey revealed that patients with COPD often underestimate the severity of their illness. Exacerbations of COPD account for 35–45% of the total per capita healthcare costs for COPD; however, these costs vary considerably with the severity of the exacerbation as well as the severity of COPD.

COPD in special populations

Although COPD has for a long time been considered a disease of old Caucasian men, recent data from the US show that mortality is rising faster among women and African-Americans. In a recently published study describing the characteristics of patients with COPD from a research database, Caucasians had less loss of lung function per pack-year smoked than African–Americans which was also less in men than women suggesting that indeed African–American women are most susceptible to the ill effects of smoke compared to other groups of men and women. Findings from the Confronting COPD International Survey, also indicate that gender differences in COPD care and outcomes do exist and need to be further explored. Women with COPD were less likely to have had spirometry testing, but more likely to have received smoking cessation advice. Furthermore, women were more likely to report severe dyspnoea, had similar cough but less sputum production than men. While any patient above the age of 40 is at risk of this disease, patients with advanced age are at higher risk of complications and increased morbidity from this disease. A report from the obstructive lung disease in northern Sweden studies demonstrated that almost 50% of elderly smokers fulfilled the criteria for COPD according to both the BTS and GOLD guidelines. However, while guidelines recommend the use of a post-bronchodilator ratio of forced expiratory volume in 1 s (FEV1)/FVC <70% to define COPD, the physiologic cutoffs for the defining COPD in elderly patients is still unknown. Furthermore, COPD in the elderly is associated with impaired health status which may not necessary be predicted by lung function tests. Important determinants of health status in this population include activity of daily living (ADL) and emotional status.
Clinical manifestations and diagnosis of COPD

The clinical presentation of patients with COPD is far from uniform. This fact has been very well described in several classic publications in the British Journal of Diseases of the Chest.\textsuperscript{3,28–30} Most patients with COPD present in the fifth or sixth decade of life although patients with alpha1-antitrypsin deficiency may present at a younger age.\textsuperscript{4,5} Furthermore, symptoms of COPD vary among patients. While most patients with COPD present with symptoms of cough and shortness of breath on exertion, many others have minimal symptoms early in their disease process. Several screening questionnaires have been developed for use in everyday clinical practice to facilitate the diagnosis of COPD in a primary care setting.\textsuperscript{31–33}

A complete assessment of a COPD patient should include physiologic measures of lung function. Spirometry is the most widely used and feasible test which can be performed in the primary care setting.\textsuperscript{34} The diagnosis of COPD is made if the post-bronchodilator FEV\textsubscript{1}/FVC ratio is <70\% although the FEV\textsubscript{1}/FEV\textsubscript{6} ratio may be used as an alternative as it has been shown to correlate with FEV\textsubscript{1}/FVC.\textsuperscript{35} Evaluation of acute bronchodilator response should not be used alone as an index to differentiate asthma from COPD as many patients with COPD demonstrate significant reversibility to acute bronchodilator administration.\textsuperscript{36} Other tests of lung function such as measurement of lung volumes (e.g.; inspiratory capacity at rest and during exercise) can shed more details on the physiologic abnormalities present in COPD although such tests are rarely needed on routine assessment.\textsuperscript{37,38} Exercise intolerance in patients with COPD can be assessed either by measuring the walking distance (e.g., six minute walk test) or by performing formal exercise testing using treadmill or cycle ergometry.\textsuperscript{39–41}

Diagnosis of COPD in the community is more likely in patients with worse lung function and health status and in patients who are symptomatic.\textsuperscript{42} However, attaining a correct and early diagnosis in the primary care setting remains challenged by the delay and infrequent use of spirometry in that setting due to lack of adequate training in its use and interpretation.\textsuperscript{43} This is compounded by the lack of knowledge about COPD by patients at risk such as heavy smokers.\textsuperscript{44} Furthermore, there is no clear correlation between symptoms, effort intolerance, and objective measures of lung function.\textsuperscript{45,46} This has been clearly described in a classic article published in the British Journal of Diseases of the Chest in 1961 which studied a group of in-patients with chronic obstructive airway disease attending the London Chest Hospital.\textsuperscript{45} Despite being a pilot study, this manuscript sets out to grade the severity of disease and assess the clinical value of using various tests in patients with "chronic obstructive airways diseases". The authors studied effort intolerance, lung function, arterial blood gas analysis and exercise desaturation and suggest that assessing severity of the disease should include more than one measure. It is of interest that 60 years later, grading the severity of COPD continues to be an important clinical dilemma. While current guidelines suggest using the percent predicted FEV\textsubscript{1} to assess severity of the disease, recent studies suggest that the use of multidimensional grading systems may be more useful in assessing the severity and impact of COPD.\textsuperscript{47} Furthermore, the use of radiological studies to evaluate the lung parenchyma and airway wall thickness may aid in differentiating between the different COPD severity phenotypes.\textsuperscript{48,49}

Management guidelines for COPD

Several guidelines for the management of COPD have been published.\textsuperscript{50–56} While the main goals for these guidelines are to achieve better standards for the diagnosis, treatment and prevention of COPD, unfortunately these guidelines have not been widely implemented.\textsuperscript{55–57} Furthermore, primary care physicians who treat the majority of patients with COPD often find the guidelines complicated and thus show a major gap in the knowledge of all core elements of these guidelines.\textsuperscript{57} A major problem with existing guidelines is that they are usually based on efficacy and not on effectiveness studies, and do not properly focus the process of behavioural changes of health professionals and patients.\textsuperscript{56} Furthermore, as rapid changes may occur in the treatment of COPD, future guidelines should be able to adapt to these rapid adjustments.

Prognostic factors and health outcomes in COPD

COPD has a progressive course especially in patients who continue to smoke. Several studies have addressed risk factors associated with progression of COPD.\textsuperscript{58–60} Early studies performed on case series of patients with COPD, demonstrate that the severity of airflow obstruction, hypoxaemia, hypercapnia and dyspnoea, and the presence of co-morbidities such as congestive heart failure are important indicators of poor prognosis in COPD.\textsuperscript{59,60} A more recent paper described important gender differences in the predictors of decline of lung function in mild to moderate COPD.\textsuperscript{58}

Although lung function remains the most important objective outcome in assessing the severity and prognosis of patients with COPD, success of treatments for this disease is usually evaluated by measuring the impact of such treatments on a range of patients health outcomes.\textsuperscript{61,62} The course of patient reported outcomes such as health status, dyspnoea and psychological status often deteriorate significantly over time and may not strongly correlate with changes in lung function parameters such as FEV\textsubscript{1}.\textsuperscript{63} Change in symptoms of COPD is an important health outcome although cannot be accurately measured. The Breathlessness, Cough and Sputum Scale was shown to be a reliable, valid and responsive patient-reported outcome measure of symptom severity in patients with COPD and can be used in clinical trials.\textsuperscript{64,65} Several instruments to measure health status were developed, tested and validated in patients with COPD.\textsuperscript{66–72} Health status in COPD correlates with severity of the disease and hypoxaemia, and the presence of co-morbidities.\textsuperscript{73} One study which compared the responsiveness of six instruments used to measure health status, confirmed that the Chronic Respiratory Questionnaire (CRQ) and the Saint Georges Respiratory Questionnaire (SGRQ) were substantially more responsive than generic measures, and suggested particularly strong responsiveness for the self-administered CRQ.\textsuperscript{67} ADL may be severely
COPD is a multicomponent disease. These components affect the lungs and organs outside the lungs. The impact of the systemic co-morbidities of COPD is substantial, and although some studies have addressed the potential mechanisms underlying these co-morbidities, many important questions remain to be answered. Systemic manifestations of COPD include musculoskeletal, psychological, nutritional depletion, anaemia and sexual dysfunction. Other pulmonary co-morbidities of COPD include cardiovascular complications and pulmonary hypertension, obstructive sleep apnoea and lung cancer. Thus a comprehensive assessment of a patient with COPD should also include assessing the systemic co-morbidities of this disease.

Acute exacerbation of COPD

Acute exacerbation of COPD is associated with increased morbidity and mortality. A variety of definitions for acute exacerbation of COPD have been used in clinical studies. These have been traditionally based on change in patients' symptoms or their requirement for antibiotic therapy, oral steroids or hospitalization. The importance for a standard definition has been recently emphasized. From a recent survey from 1100 subjects with symptoms compatible with COPD, exacerbations generated a mean of 5.1 medical visits/year (SD = 4.6) with the mean duration of exacerbation symptoms being 10.5 days. Increased coughing was the exacerbation symptom having the strongest impact on well-being (42%). Fifty-five percent of patients declared that quicker symptom relief was the most desired requirement for treatment.

The role of bacterial and viral infections as causative factors of acute exacerbation of COPD was extensively described in several publications over the last 50 years. In one of these classic publications, Calder et al. described their experience from a 5-year study of prophylactic antibiotic therapy in patients with chronic bronchitis. In that study, the use of prophylactic antibiotics reduced the number of exacerbations and the isolation of sputum pathogens; however, it did not influence the rate of decline in ventilatory function. This was one of the very first longitudinal studies that utilized what later became the gold standard outcome in assessing the natural history of the disease; the decline in lung function.

Many patients with acute exacerbation of COPD may need hospitalization. The presence of concurrent diseases such as heart disease and pneumonia prolong the hospital episodes of COPD patients and the use of long-term oxygen therapy (LTOT) and of short-acting β-agonists were associated with a late recovery from acute exacerbation of COPD. Factors that have been associated with re-admission for acute exacerbation of COPD include: hospital admission within 1 year prior to the current exacerbation, nursing home residency, dependency in self-care activities, right heart strain pattern on electrocardiogram, the use of high doses of inhaled corticosteroids (ICSs) and a serum bicarbonate level > 25 mmol/l.

Management of COPD

Recent research has focussed on examining the multi-component nature of COPD (including impairments of metabolism and inflammation) more carefully, and determining the effects of treatment on both the systemic and physiological aspects of COPD. In effect, the multi-component nature of COPD has provided a challenging environment in which to develop successful treatments.

Obviously, many questions remain to be answered, but a comprehensive approach is now considered essential to the life-long management of COPD, and will undoubtedly reduce the considerable socio-economic burden of COPD. At present time, a combination of pharmacological and non-pharmacological approaches seems to be effective in the attempt to face with these problems.

Pharmacologic management

Pharmacologic management for COPD includes antibiotics, bronchodilators, corticosteroids, and mucolytics. There are also some other classes of drugs that are still considered of minor importance, but worthy of clinical investigation.

Antibiotics

In 1943, May published an article in which he documented that the concentrations of penicillin attainable in the sputum of patients with chronic bronchitis or bronchiectasis were correlated with the in vitro sensitivity to penicillin of the infecting organisms and the clinical and bacteriological response of the patients to treatment. This observation was really interesting and nowadays it is still relevant. In fact, today we consider the interrelationship between pharmacokinetics and pharmacodynamics extremely important in choosing the appropriate antibiotic and the dosage regimen for treating acute exacerbations of chronic bronchitis. It must be highlighted that in May's paper each penicillin regime investigated gave sputum levels higher than the sensitivity level of pneumococci, which responded satisfactorily to all penicillin preparations. Unfortunately, during the ensuing decades, penicillin-resistant pneumococci has become an area for great clinical concern worldwide because it has been associated with treatment failure.

Up to 1980, the journal published a large amount of papers on the use of antibiotics in the treatment or prophylaxis of acute exacerbation of chronic bronchitis. In effects, at that time there was a lot of interest for the antibiotic therapy. This likely happened because the "British hypothesis", which raised the concept that chronic bronchitis could predispose to infection, which in turn damaged the airways and/or the alveoli, leading to progressive airflow limitation. The continuous introduction into the market of new anti-infective agents certainly facilitated the...
production of data relating to the use of such agents. Unfortunately, most of these clinical trials of antibiotics have compared new drugs with standard therapy in patients with exacerbations who, in most cases, would have never required an antibiotic if treated in real-life conditions. In general, these studies might have been required for the pharmaceutical companies to launch their new antibiotics, but offered limited, if any, useful information to the clinician. In any case, May\textsuperscript{105} wrote a review that was really important for those times. He described in extremely critical manner the problems related to the bacteriology and chemotherapy of chronic bronchitis. In his conclusions, May expressed an anticipatory view. It was his opinion that it was possible that failure of penetration of antibiotic into mucoid bronchial secretions in patients whose infection was controlled by bacteriostatic therapy might explain the failure of such therapy to give more lasting benefit. If the organisms in the secretions were inaccessible to the antibiotic, and there were no phagocytes present, there was no reason why they should not remain viable indefinitely and able to cause a fresh infection as soon as the bronchial tissue was freed from protective antibiotic. For this reason, he suggested that the approach to chemotherapy of chronic bronchitis had to change from bacteriostatic, which was common at that time, to bactericidal and, consequently, and able to cause a fresh infection as soon as the bronchial tissue was freed from protective antibiotic. For this reason, he suggested that the approach to chemotherapy of chronic bronchitis had to change from bacteriostatic, which was common at that time, to bactericidal and, consequently, treatment courses had to become intensive but for short period. Interestingly, several articles\textsuperscript{108,111,117,122} have reported that chemoprophylaxis was of no help in preventing acute exacerbations of pulmonary infection although the attacks were milder in nature and the total number of monthly purulent sputum specimens was less in the group given a prophylactic antibiotic, it had no effect on time off work in individual spells of illness and, moreover, it did not influence the rate of deterioration in ventilatory function. It would be interesting to know why in the following years many researchers have spent time and money for getting the same conclusions!

Even in the last few years, \textit{Respiratory Medicine} has published some papers devoted to the use of antibiotics in the treatment of acute exacerbation of chronic bronchitis.\textsuperscript{128–139} Also these studies, however, might have been required for the pharmaceutical companies to launch or support their new antibiotics (gemifloxacin, moxifloxacin, telithromycin), but offered limited, if any, useful information to the clinician. Nonetheless, it must be highlighted that Banerjee et al.\textsuperscript{136} reported that treatment of COPD with clarithromycin during the clinical stable state yields no clinical advantages and therefore cannot be recommended as means of eliminating sputum bacteria or preventing infective exacerbations. This does not seem an unexpected result that fits well with the prescriptive behaviour of general practitioners. Miravitlles et al.\textsuperscript{137} published interesting data coming from a Spanish cross-sectional observational study of ambulatory COPD patients. Treatment for exacerbations included inhaled bronchodilators (90%), antibiotics (89%), ICSS (71%) and oral corticosteroids (43%); the number of previous acute exacerbations was the main factor associated with exacerbation treatment except for oral corticosteroids, the use of which was associated with more impaired pulmonary function. More intriguing is the Hasani’s\textsuperscript{138} paper, which showed that even only 7 days antibiotic treatment slightly improved tracheobronchial clearance and significantly decreased cough suggested a significant role of the antibiotic treatment at least in decreasing the risks of further and greater damage to the airway epithelium. In any case, pneumococcal vaccination reduces the risk of \textit{Streptococcus pneumoniae}-induced COPD exacerbations.\textsuperscript{139}

**Bronchodilators**

The article by Feinman and Newell\textsuperscript{140} published in 1963, was the first paper in the journal to focus on the use of bronchodilators for treating an obstructive airway disease. It had the great merit of documenting that isoprorenaline in a dose of 0.4 mg delivered by a self-propelled aerosol device, gave an improvement in FEV\textsubscript{1} on average 0.10 L better and an improvement in VC 0.16 L better than 3 min continuous inhalation of 1% isoprorenaline solution using a standard hospital nebulizer driven by an oxygen cylinder. The authors recognized that eventhough these differences were not large or important clinically, the much smaller dose given by the self-propelled aerosol device reduced the chance of side effects and justified rejection of the more standard methods of administration that were popular at that time.

The development of newer bronchodilators at the end of 1970s slowly moved the interest of the journal towards this new therapeutic option.\textsuperscript{141–148} Berend et al.\textsuperscript{141} documented that the bronchodilator response to salbutamol by intermittent positive pressure ventilation (IPPV), was greater than by metered dose inhaler (MDI) only in patients suffering from chronic obstructive bronchitis with severe airways obstruction and little additional benefit was gained with the 10 mg dose. Jenkins and Moxham\textsuperscript{147} suggested that there is minimal if any benefit in terms of functional status administering regular doses above the equivalent of 200 µg of salbutamol four times daily in COPD, although pulmonary function (FEV\textsubscript{1} and PEFR, but not FVC) results showed a trend towards higher doses producing improved response and a longer duration of action, with bronchodilation following 2 mg significantly greater than 400 µg salbutamol. This study was broadly a forerunner of the actual tendency to use greater than traditional dosage of long-acting β\textsubscript{2}-agonists (LABAs), mainly formoterol, to prolong their duration of action.\textsuperscript{149}

After 1989, the number of articles that have explored the use of bronchodilators in COPD increased in a dramatic manner. It is almost impossible to quote all these articles, and, consequently, only those papers that in our opinion have been innovative, will be discussed. Hansen et al.\textsuperscript{150} and Hansen and Andersen\textsuperscript{151} in 1994 and 1995 published two interesting papers that documented that the replacement of nebulizers with multidose dry powder inhalers was advantageous both for the COPD patient, in terms of ease of use and portability, and for the Local Health Service, in terms of reducing resources spent on inhalation treatment. Cazzola et al.\textsuperscript{152} in 1995 published one of the first articles on the use of LABAs in the treatment of COPD. Up to 2000, the majority of these articles have been focused on the activity of LABAs\textsuperscript{153–157} and the possibility of combining these agents with bronchodilators of other classes.\textsuperscript{158,159} Importantly, an editorial published in 1999\textsuperscript{160} raised for the first time the question of considering LABAs an alternative first choice option for the treatment of stable COPD.
More recently, the interest of researches has been focused on inhaled long-acting bronchodilators, although some interesting new observations on short-acting bronchodilators have also been published. Particularly, the documentation that prescription of ipratropium was associated with increased mortality in both COPD and asthmatic patients. Moreover, there have been two interesting papers on the use of theophylline, now considered a third line agent in the therapy of COPD. In particular, Ram et al. have published an evidence-based review that has shown that theophylline continues to have a role in the management of stable COPD, and is preferred by patients over placebo. However, the benefits of theophylline in stable COPD have to be weighed against the risk of adverse effects. The documentation that tolerance to pharmacologic bronchodilation occurs with LABAs such as salmeterol and not with long-acting inhaled anticholinergics such as tiotropium is a really intriguing finding. It must be highlighted that the reported diminishment of bronchodilator responses was relatively small, and a prospective trial designed specifically to examine for tolerance should be designed. Nevertheless, the concept of tolerance may need to be considered when re-evaluating COPD patients during chronic treatment with LABAs, considering the possibility of using bronchodilators of different classes. Adams et al. have documented that once-daily tiotropium provides significant improvement in lung function, health status, and dyspnoea when used as maintenance therapy in undertreated COPD patients who were not previously receiving maintenance bronchodilator therapy. In any case, although this potentially important problem, Jones et al. have observed that addition of salmeterol to COPD patients’ current therapy improved lung function, health status at the expense of a modest increase in costs compared with usual therapy. Considering the fact that both LABAs and tiotropium are effective agents in the treatment of stable COPD, the present trend is to combine a LABA and tiotropium.

The fast onset of action of formoterol has suggested testing this bronchodilator in the treatment of acute exacerbation of COPD. Preliminary data with LABAs seem to indicate that repeated doses of both formoterol and salmeterol induce an effective dose-dependent increase in lung function in patients suffering from COPD exacerbations, but only formoterol induces a fast onset of action. A suggested possible alternative to the use of higher than recommended dose of formoterol is the combination of formoterol and tiotropium, although the course of the effects of these drugs differs significantly from that in stable COPD, with a shorter bronchodilation both for tiotropium and formoterol. In any case, because of its pharmacodynamic profile with both a rapid onset of effect, similar to salbutamol, and a long duration of action, similar to salmeterol, formoterol is suitable for both maintenance and as-needed treatment in COPD.

Corticosteroids
In 1958, Ogilvie published an article on the treatment of patients with severe asthma and chronic bronchitis. This article was surely significant at that time because it had the merit of stressing the fact that the treatment of patients with severe asthma and chronic bronchitis was perfectly feasible, and success might be expected in two-thirds or more of cases. Moreover, it highlighted the importance of calculating the cost because it was becoming increasingly clear that there was an imperative need to reduce the cost of certain remedies of proved and vital importance, whether by a vast increase in the scale of production, or by other means. Unfortunately, Ogilvie considered the treatment of severe asthma and chronic bronchitis in the same manner and suggested that it had to consist of the suppression, first of all, of ineffective activity by antibiotic therapy, followed by the exhibition of a suitable adrenal hormone in adequate dosage. This initial treatment had to be followed by maintenance therapy, but it was Ogivie’s opinion that it could fail within 6 months if it consisted of hormone alone (mainly, ACTH or prednisone). Consequently, successful maintenance treatment of persistent asthma with chronic bronchitis depended on the use both of antibiotics and hormones on a permanent or semi-permanent basis. In any case, this paper could be considered important still today because it stressed that the use of “antispasmos” (adrenaline hydrochloride 1 in 1000 by injection, aminophylline by mouth, and what he just defined a new aerosol solution which he was testing prior to introduction for general use) was ineffective in a number of patients that, on the contrary, responded very well to hormone treatment. This is one of the first reports that patients suffering from chronic bronchitis may present an irreversible airway obstruction, although today this information is considered misleading. On the contrary, the documentation that the use of bronchodilators as a screening device for the selection of patients for hormone treatment is valueless is still relevant. In 1960, Ogilvie and Newell tested a maintenance combined treatment with an oral corticosteroid (methylprednisolone) and an antibiotic (tetracycline-tab滋oedrin) in a series of asthmatics with chronic bronchitis. They concluded that maintenance treatment by corticosteroid had some clinical effect on certain of these patients, which was annulled by discontinuing it, a view supported by the frequent clinical observation that deterioration in the chronic asthmatic with chronic bronchitis occurs much more readily than the reverse change. This was an intriguing conclusion that is still relevant considering the existing debate on the use of corticosteroids in stable COPD.

In 1963, Hurford et al. explored the use of prednisolone in chronic bronchitis. They observed that only a small proportion (20%) of patients with chronic bronchitis and emphysema who did not react to more conservative treatment showed a response to a week on prednisolone at a dose of 30 mg a day and raised the suspicion that these responders were characterized by something different which would explain their heterogeneity. The authors also observed that some patients, who did not respond in the shorter period, responded to corticosteroids after longer periods than one week. Discussing these results, they highlighted a concept that is still a controversial issue, although it is supported by many researchers in the field. It was their opinion that if there are occasional cases of chronic bronchitis in which endobronchial changes and bronchospasm will be relieved by prednisolone, they are probably much fewer than would appear if this drug is used without close control with ventilatory tests. There is no
doubt that it can temporarily bring a general feeling of well-being which will lead some patients with chronic bronchitis to feel better able to carry on despite virtually unchanged exercise tolerance. But this is certainly not sufficient excuse for continuing the use of corticosteroids.

In the 1990s, some articles that related the use of corticosteroids were published. Sendorovitz et al. documented that in outpatients with stable COPD and no signs of asthma or atopy, 2 weeks treatment with prednisolone seems to be of no value in choosing subsequent long-term therapy. Ström reported an increased mortality in women receiving oral corticosteroid medication that was found to be associated with an increased need of hospital care due to longer hospital stays during the terminal stage of the disease. This finding has an important clinical impact. In fact, since prescriptions of the same dose of oral corticosteroid medication to male and female patients in COPD could result in a greater incidence and severity of side-effects in female patients, this practice should be debated. Jarad et al. were able to document that abrupt withdrawal of ICSs may lead to early exacerbation in stable COPD. This is an important finding because it indicates that clinicians should be aware of the risk of an exacerbation developing within a few weeks of stopping this treatment and, consequently they should never suggest to patients to discontinue treatment with ICSs if this is not giving them immediate benefit.

Some interesting papers have focused on the administration of ICSs to COPD patients. They reach contrasting results and, consequently, they confirm the debate existing on this topic. Thus, it has been documented that early initiation of ICS treatment does not seem to affect the progressive deterioration of lung function or other respiratory health outcomes in subjects with early signs and symptoms of COPD. Therefore, primary care physicians should be careful to base maintenance treatment with ICSs in subjects at risk for, or in an early stage of COPD on a single spirometric evaluation performed in the first months of treatment. However, Ayres et al. reported that treatment with an ICS was associated with statistically significant clinical benefits in patients with moderate-to-severe COPD currently symptomatic on regular bronchodilator therapy. As the differences in direct and total costs compared with placebo were small and non-significant, they considered such a type of treatment cost effective in this patient population. Moreover, Tkacova et al. documented that ICS may reduce all-cause mortality in patients with severe COPD and chronic hypoxaemia, who require long-term domiciliary oxygen therapy. These data suggest that ICS may indeed play an important role in improving clinical outcomes in patients with advanced COPD.

Combination therapy

The benefit that exists when an ICS is combined with a LABA has been discussed in several articles. Analysing results of the TRISTAN study, Vestbo et al. did not find differences between women and men with COPD in the efficacy and safety outcomes in comparing the salmeterol/fluticasone propionate combination versus placebo. Cazzola et al. suggested that when treating patients with formoterol, it is prudent to check their arterial blood gases because this bronchodilator can worsen pretreatment hypoxaemia. However, combined administration of formoterol and budesonide reduces the potential for acute effects of formoterol on blood-gas tensions. Mapel et al. analysed COPD patients from two different managed care organizations from different parts of the United States and found that patients who used an ICS, a LABA, or an ICS plus a LABA had better survival than patients who were only using short-acting bronchodilators, and that this survival benefit was preserved even after adjustment for the other clinical factors likely to affect survival, including age, disease severity, comorbid diseases, and smoking history. They found that COPD patients who had a concurrent diagnosis of asthma had better survival than those who did not, but the benefits of ICS therapy with or without a LABA were preserved after adjusting for asthma in the models. Interestingly, LABA and the combination treatments are likely to be cost-effective, at least in the United States.

Mucolytics agents

Several papers on the use of mucolytics agents in COPD were published. In particular, Millar et al. were unable to find significant differences in lung function, mucociliary clearance curves or sputum viscosity following treatment with N-acetylcysteine (NAC) compared to control or placebo measurements. Even more important, Parr and Hultson failed to find any statistically significant difference in the number of exacerbations between NAC or placebo groups after a 6-month treatment, although there was a slight trend towards improvement in the NAC group during the first 3 months of the trial. It must be highlighted that the dosage of NAC used in these studies was really low (200 μg thrice daily). The possibility of influencing tracheobronchial clearance and in this way, eliciting a beneficial action in chronic bronchitis was tested again administering NAC. However, NAC administered by MDI did not have any significant effect on patients’ feeling of well-being, sensation of dyspnoea, intensity of coughing, mucus production, or expectoration or lung function, although another study documented that orally administered NAC may improve general well-being in patients with mild chronic bronchitis. Considering these findings, it is not surprising that a large randomised placebo-controlled long term (3 years) trial of the effects of NAC 600 mg on a once daily basis on the progression of disease and exacerbation rate in patients with COPD who had frequent exacerbations (i.e., at least two per year for 2 years) confirmed that NAC at the dosage of 600 mg daily is ineffective at prevention of deterioration in lung function and prevention of exacerbations in patients with COPD.

These results do not support the use of this drug in COPD, but there has been recent evidence that NAC may be considered an antioxidant rather than a mucolytic agent. Interestingly, van Schayck et al. hypothesized that that anti-oxidant treatment might be relatively more effective among those COPD patients who respond less well to ICSs (low reversibility and heavy smoking).

Alternative drugs

Considering the need for alternative drugs in the treatment of COPD, in the last few years the journal published some
small, but intriguing, articles, which described the efficacy of several different new therapeutic possibilities. These range from the potential of prescribing montelukast in elderly patients with moderate to severe COPD, to the use of selective phosphodiesterase (PDE)4 inhibitors (ciloramilast and roflumilast) due to their novel mechanism of action and potent anti-inflammatory effects, coupled with a good safety and tolerability profile, or to the use of a low-dose testosterone to men with COPD in order to counteract progressive weight loss, and loss of lean body mass that has specifically been associated with skeletal muscle dysfunction and is frequent in COPD patients. Recently, Gronke et al. have shown that H1 receptor antagonist cetirizine was able to influence hypertonic saline-induced airflow obstruction in moderate-to-severe COPD. In view of the mechanisms involved in hypertonic saline responses, it is an open question whether stronger effects can be elicited with higher doses and whether such effects would translate into clinical benefits, e.g. during exacerbations. The documentation that rebamipide, a gastro-protective agent used in the treatment of gastrosis and ulcerative colitis, is able to prevent TNF-α release, neutrophil recruitment into the airways, and MUC5AC mucin synthesis in cigarette smoke-stimulated airway epithelium, is another intriguing finding because it suggests that rebamipide may be used to treat mucus hypersecretion in cigarette smokers.

Chronic respiratory failure is the end stage of COPD. Home oxygen therapy is the only treatment which has been demonstrated to improve survival of COPD patients with chronic respiratory failure, but the mortality of patients receiving LTOT is around 50%. These poor results have spurred the search for coadjuvant or alternative pharmacological treatments. Almitrine bismesylate is a peripheral chemoreceptor agonist which is believed to improve oxygenation, probably by improving the ventilation perfusion mismatch. Although when used at doses of 100–200 mg/day it shows an improvement in PaO2 greater than 5 mmHg, its tolerance is poor, and the number of side-effects such as dyspnoea and peripheral neuropathy was unacceptable. For this reason, it has been tested at doses of 1 mg/kg/day using an intermittent schedule in a randomized double-blind placebo-controlled study, but while well tolerated, at these doses, use of almitrine is not effective in long-term treatment of chronic hypoxaemia in COPD patients. Nonetheless, in short-term treatment, the association of almitrine and medroxyprogesterone acetate seems to be more efficient than either drug alone at improving arterial blood gases in these patients. Moreover, it has also been documented that four days of treatment with almitrine improved gas exchange in a group of subjects with hepatic cirrhosis.

Non-pharmacologic management

Non-pharmacologic management for COPD include LTOT, nasal positive pressure ventilation (nPPV), pulmonary rehabilitation and lung volume reduction surgery (LVRS). In the future, it will be important to establish the precise value of the different management strategies available for COPD—evaluating both clinical and physiological endpoints and using the data to more accurately define candidate patients accordingly. The challenge will be to develop this base of knowledge in order to shape future research and allow clinicians to deliver tailored COPD management programs for the growing number of patients afflicted with this disease.

Developing the means to measure the effects of COPD is important, both in terms of understanding disease pathophysiology for research purposes, and accurately assessing the effects of treatment on the patient. Future developments will include computerizing these methodologies to permit faster and more individual patient-centred measurements.

Long-term oxygen therapy (LTOT)

Apart from smoking cessation, LTOT is the only treatment to date which has been shown to modify the long-term decline in lung function that is associated with COPD and, therefore, improve survival rates in severe cases; thus its role in COPD is well defined.

LTOT has also been associated with a variety of benefits in patients with severe COPD, including increased survival, reduced secondary polycythemia, improved cardiac function during rest and exercise, reduction in the oxygen cost of ventilation and improved exercise tolerance. Of particular note are the results of a longitudinal study showing that LTOT significantly improved heath-related quality of life (HRQoL) at 2 and 6 months, compared with a progressive decline in HRQoL in the non-LTOT group. In the LTOT group, 67% and 68% of patients (at 2 and 6 months, respectively) showed a clinically significant improvement in their CRQ scores. Hence, there is a convincing rationale for including LTOT in the treatment paradigm for patients with severe COPD. Patients with PaO2 < 7.3 kPa (55 mmHg; corresponding to SaO2 < 88%) whose disease is stable despite receiving otherwise comprehensive medical treatment should receive LTOT. A patient whose PaO2 is 7.3–7.8 kPa (55–59 mmHg; SaO2 89%) should receive LTOT if they show signs of pulmonary hypertension, cor pulmonale, erythrocytosis, oedema from right heart failure or impaired mental state. If oxygen desaturation only occurs during exercise or sleep, then oxygen therapy should be considered specifically under those conditions. An optimal medical regimen can be established incorporating these guidelines, with the chief aim of achieving an optimized ventilation:perfusion ratio matching (V/Q) as a means of correcting hypoxaemia.

COPD patients undergo episodes of O2 desaturation of arterial blood during rapid eye movement sleep. Fletcher et al. revealed that these desaturations occur both in non-hypoxemic patients and in patients who are hypoxemic during the day. Further research by Plywaczewski et al. showed that 47.6% of COPD patients treated with LTOT spent > 30% of the night with a SaO2 of < 90%, and thus required increased oxygen flow during sleep. The administration of oxygen at a flow-rate higher than the daytime setting usually corrects nocturnal hypoxaemia. Conflicting evidence surrounds the contention that patients who only desaturate during sleep will benefit from nocturnal oxygen treatment. But while Fletcher et al. found a beneficial effect of supplemental oxygen treatment in this patient group, other well-controlled studies have not shown that the use of nocturnal supplemental oxygen alters mortality or clinical
course, other than slightly lowering pulmonary artery pressure.

Oxygen therapy during exercise decreases dyspnoea and improves exercise tolerance at submaximal exertion. The mechanical rationale underlying this observation is a decrease in dynamic hyperinflation, and reduced ventilatory drive. LTOT is prescribed for patients who become more hypoxic during exercise, or who only become hypoxic during exercise, with oxygen settings determined while the patient is undergoing a typical level of exertion. Studies evaluating the long-term benefit of oxygen treatment solely for exercise have yet to be conducted.

In an interesting paper published in 1989, a total of 43 severely ill COPD patients already on 24 h, or near 24 h, per day supplemental O2 were randomly assigned to transtracheal oxygen delivery (n = 22) or usual delivery of O2 by nasal cannula or face mask (n = 21). A few important changes were found in pulmonary function over time such as decreases of PEFR, FEF and MVV for both experimental and control groups, and FEV₁% and FEV₃% in experimental patients. At the same time, there was a significant decrease in both haematocrit and haemoglobin, and per cent shunting for the experimental group and a significant increase in per cent shunting in the control group. Physical, social and psychological assessments showed significant improvement over time for experimental patients and declines for the control group. Lastly, medical costs were positively affected, as fewer days were spent in hospital post-study enrolment by experimental than control groups, and post-enrolment relative to pre-enrolment by experimental patients.

Non-invasive ventilation
Mechanical ventilation increases or substitutes for an individual’s spontaneous respiration, as in the case of acute respiratory or ventilatory pump failure. Non-invasive ventilation, e.g. intermittent negative pressure ventilation (INPV) or nPPV, have recently re-emerged as popular options that avoid the risks associated with invasive ventilation. nPPV is thought to assist ventilation, by improving inspiratory flow rate and correcting hypoventilation. Other possible mechanisms of action include resting respiratory muscles and resetting the central respiratory drive.

In contrast to the evidence supporting the use of nPPV to tackle other causes of chronic respiratory failure, there is conflicting evidence regarding the benefits of nPPV in COPD. In a 12-week double-blind study of 184 patients with severe COPD, no significant difference was observed in 6-min walk test results, cycle endurance time, severity of dyspnoea, HRQoL, respiratory muscle strength or arterial blood gas compared with sham treatment. This suggests that inspiratory muscle rest has no benefits for patients with severe stable COPD, although poor patient compliance may have contributed to the results.

Regarding the administration of nPPV in patients with severe COPD, two 3-month crossover trials of similar design came to different conclusions. The discrepancy between these results may be explained by the difference between patient sets at baseline: patients with greater CO₂ retention and more frequent nocturnal oxygen desaturations may benefit more from nPPV administration.

In addition to this conflicting data on physiological endpoints there is a lack of data showing whether nPPV treatment actually improves survival rates. Two large multicentre trials have focused on nPPV in patients with severe hypercapnic COPD. One trial published as an abstract by Muir et al. which compared home nPPV plus LTOT with LTOT alone, indicated that there is no overall survival benefit in patients receiving nPPV plus LTOT, although there may be a slight improvement in survival for patients over 65 years of age. A 2-year Italian multicentre study also examined the effects of nPPV plus LTOT compared with LTOT alone (N = 122). In this trial, nPPV plus LTOT improved PaCO₂ during breathing of the usual oxygen inspiratory fraction. Long-term improvements were also noted in dyspnoea and HRQoL in the nPPV plus LTOT group, but survival was similar between treatment groups.

Currently, there is little evidence supporting the use of mechanical ventilatory support in the routine management of COPD. However, further large studies may be able to identify subsets of patients for whom nPPV would be beneficial.

An historical and pioneering paper published in 1958 showed that inspiratory positive pressure breathing (IPPB) by itself and independently has therapeutic value, particularly in asthma, bronchitis and emphysema, concluding that it probably accomplishes this result by helping to clear the bronchial airways of obstructing secretions and exudations, although other effects as yet unknown may be important. The therapeutic results are erratic and the use of IPPB is justified only by the otherwise inexorable progress to an asphyxial death of crippling COPD. The authors suggest that this technique may also be used as a means of temporarily diminishing venous return in acute pulmonary oedema, and of expanding collapsed segments of lung in respiratory paralysis and post-operative immobilization of the lung and they retain that the hazards of this form of treatment are slight.

LVRS for emphysema
LVRS was originally proposed as a palliative treatment for patients with severe emphysema. The rationale for LVRS is based on the premise that these patients have severe hyperinflation and the goal of surgery is to remove functionally useless emphysematous lung. Generally, this involves the removal of 25–30% of lung tissue from both the left and the right sides. Benefits associated with LVRS are improved lung function (reduced lung volume and increased FEV₁) and exercise (including the distance walked in 6 min). Although carefully selected patients benefit from LVRS, questions remain concerning the magnitude and duration of positive outcome.

The National Emphysema Treatment Trial (NETT) was set up as a multicentre, randomized, large-scale clinical trial (N = 1218) to evaluate the effects of LVRS. Overall results from the NETT at 2-years post-randomization indicate that LVRS improves exercise capacity, but does not improve survival compared with medical therapy. Patients in the LVRS group also reported improved health status and less dyspnoea compared with the medical group. Subgroup analyses showed that patients with upper-lobe predominant emphysema and low exercise capacity had improved survival.
with LVRS, compared with medical therapy; those patients with\textsuperscript{245} mainly non-upper-lobe emphysema and high exercise capacity showed reduced survival. From these results, two key outcome predictors can be identified: distribution of emphysema and exercise capacity following pulmonary rehabilitation. Combined with the factors placing patients at high risk for LVRS, these predictors allow more targeted patient selection than was previously possible.

Key questions remaining concern the role of pre-operative pulmonary rehabilitation, the mechanisms by which LVRS improves lung function and survival, and the impact of different surgical techniques on LVRS outcomes.\textsuperscript{232} The identification of long-term predictors of LVRS outcomes would be a welcome development, while investigating unilateral or repeated LVRS, as well as non-invasive techniques to reduce lung volume, may prove successful in the future.

**Pulmonary rehabilitation**

Pulmonary rehabilitation complements pharmacotherapy and is now considered central to the management of symptomatic COPD.\textsuperscript{246} This form of management has negligible effects on pulmonary function, yet commonly provides substantial relief from dyspnoea, increased exercise tolerance and improved HRQoL.\textsuperscript{246} Pulmonary rehabilitation appears to work via several mechanisms, including reducing some of the comorbidity associated with chronic respiratory disease (such as the physical deconditioning associated with sedentarism) and providing patients with self-management strategies (through disease-related education).\textsuperscript{246} Rehabilitation would also seem to reduce subsequent health care utilization, with the valuable cost reductions that this would imply.\textsuperscript{246}

The logical concept of optimizing the pharmacologic management of COPD patients prior to, and during, pulmonary rehabilitation to achieve greater benefit is becoming more widely recognized. Despite a growing body of research evidence, further work is needed to determine which patients will benefit most from pulmonary rehabilitation, how this form of management is best prescribed, and how to identify the most suitable practice setting, which is dependent on the stage/phase of the disease.

Pulmonary rehabilitation is defined as an art of medical practice in which an individually tailored, multidisciplinary programme is formulated. It is indicated for patients suffering from complex problems in relation to their pulmonary disease. The goals of pulmonary rehabilitation are: (1) to decrease the physical and psychological manifestations of the underlying disease, i.e. reduce the impairment due to the disease; (2) to increase physical and mental fitness and performance, and reduce the disability; (3) to achieve maximal social reintegration of the patient, thus lowering the handicap.\textsuperscript{247} The ultimate goal is a maximal functional capacity, as allowed by the pulmonary disturbance and overall situation. The methods by which these goals may be achieved are combined in a programme tailored to each individual patient. It consists of: (a) an accurate diagnosis of the disease and of the functional limitations of the patient, (b) education about the disease, its pathophysiology, use of medications, use of a peak flow metre, and the avoidance of harmful or aggravating stimuli, e.g. smoking, (c) physical training to improve the physical fitness and performance, and (d) psychosocial support. The programme should be based on an adequate diagnosis of the extent and character of the limitations of the individual patient.\textsuperscript{247}

Pulmonary rehabilitation is a therapeutic process, which entails taking a holistic approach to the welfare of the patient with chronic respiratory illness—most commonly COPD—and is considered essential throughout the lifetime management of patients with symptomatic chronic respiratory disease. It requires the coordinated action of a multidisciplinary healthcare team in order to deliver an individualized rehabilitation programme to best effect—incorporating multiple modalities such as advice on smoking cessation, exercise training and patient self-management education, among others. As core components of pulmonary rehabilitation, exercise training and self-management education have been shown to be beneficial in improving HRQoL in patients with chronic respiratory disease. Physical training can help to reduce the muscle de-conditioning that occurs when the activity of patients is restricted by their breathlessness and fatigue, and it is often associated with an increase in patients’ HRQoL. HRQoL can also be improved by the use of self-management education, which is designed to provide the patient with the skills to manage the health consequences of their disease. In doing so, patients are better able to cope with disease symptoms, potentially leading to reduced health care costs.\textsuperscript{247}

In the last decades there was a large debate on the effectiveness of pulmonary rehabilitation and of its different components. For example, in a 1982 negative paper eight patients with chronic obstructive bronchitis and moderate disability entered a pilot study on the effects of controlled diaphragmatic breathing. They received 3 weeks of placebo physiotherapy (shoulder exercises) followed by three weeks of instruction on controlled diaphragmatic breathing. No beneficial effects were observed on exercise performance or the perceived strain of exercise.\textsuperscript{248}

Nevertheless, pulmonary rehabilitation is now supported by a solid body of scientific evidence and is widely available in North America and in Europe for patients with COPD. As a paradigmatic example, the feasibility and benefits of providing a comprehensive but cost effective pulmonary rehabilitation programme in a UK district general hospital has been reported.\textsuperscript{249} Two hundred and sixty-seven patients with respiratory disability were referred for pulmonary rehabilitation. Patients were assessed and recruited into a 7-week outpatient-based pulmonary rehabilitation programme including elements of exercise and education without longer-term maintenance. For all graduates, shuttle distance increased by 58 m (27%) and treadmill endurance time increased by 15.9 min (294%). The Breathing Problems Questionnaire proved sensitive to changes in quality of life in some domains. The Chronic Respiratory Disease Questionnaire showed significant improvements in all domains in a sub-set of 57 patients who completed it. Longer-term follow-up of 49 patients at a mean of 10.3 months following pulmonary rehabilitation revealed that previous gains in exercise performance and quality of life were maintained with improvements in shuttle walking distance of 33 m (14% over baseline) and endurance time of 16 min (280% over baseline). The Breathing Problems Questionnaire showed no
overall change but the Chronic Respiratory Disease Questionnaire showed continued improvement in a small number of patients.

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