severity of inflammation may be related to the outcome of the disease. Airway obstruction and hyperresponsiveness are known to be associated with the degree of inflammation. Therefore, it is important to investigate the relationship between airway obstruction and hyperresponsiveness and the outcome of the disease in order to obtain arguments in the discussion about the use of long-term corticosteroid treatment in asthma.

The effects of corticosteroids in patients with COPD are as yet uncertain. In general, no or only a small improvement of airway obstruction and hyperresponsiveness is found in stable patients after short-term treatment with oral corticosteroids up to four weeks. We have recently performed a randomized, 3-period cross-over, double-blind, placebo-controlled study in 9 non-allergic patients with COPD. They were treated with budesonide 1.6 mg per day for three weeks, and prednisolone 40 mg per day for 8 days. No statistical significant effects on FEV₁ and FEF₂₅₋₇₀ histamine could be observed after any treatment period. Factors mentioned as related to the short-term corticosteroid response are the degree of reversibility, eosinophilia, and atopy [4].

It is generally acknowledged that the inflammatory process in COPD is more of neutrophilic than eosinophilic origin. This neutrophilic inflammation is thought to be very little or not at all sensitive to corticosteroids. This emphasizes the importance of accurate characterization of patients in studies on the response to corticosteroids.

Many important questions are as yet unanswered with regard to longterm corticosteroid treatment of patients with COPD. Firstly, does a longterm corticosteroid response exist? Such a long-term response could be measured for instance by diminished decrease in lung function over time, and is therefore directly related to the outcome of the disease. Some indication for such a response has arisen from retrospective studies in which it has been demonstrated that the effects of corticosteroids on FEV₁ appeared after 6-24 months of treatment with prednisolone [5]. And secondly, if a long-term corticosteroid response exists, are our measurements of the effects of corticosteroid treatment correct? Perhaps the beneficial effects of corticosteroids are reflected in increased quality of life, decreased severity of symptoms, number of infections, exacerbations and admissions to the hospital, and mortality. Results of ongoing studies have to be awaited for arguments in this discussion.

**Conclusion**

Acute and short-term effects of bronchodilators and anti-inflammatory agents on airway obstruction and hyperresponsiveness are more or less known, although underlying mechanisms need further clarification. With respect to long-term treatment, it can be concluded that much intensive and time-consuming work has to be done. Focussing on at least two aspects is thereby important: the relation between number and activation of different cell types on one side, and changes and injury in lung tissue resulting in airway obstruction and hyperresponsiveness on the other side; parameters of efficacy of treatment other than FEV₁ and FEF₂₅₋₇₀, such as complaints, number of infections and exacerbations, and mortality.

**References**


**Therapeutic implications of a precise diagnosis of airflow obstruction**

C. Picado*  

Airflow limitation can be caused by a variety of lung diseases including upper airway obstruction (UAO), bronchiectasis, bronchial asthma, emphysema and chronic bronchitis. In many cases, however, a definite aetiologic diagnosis cannot be made in which case the COPD term or other elusive terms are employed to label these patients.

It is evident that in some cases a precise aetiologic diagnosis of airflow limitation may be followed by a specific treatment, as is the case when an UAO obstruction is diagnosed. Since many UAOs have specific treatment (surgery, laser therapy) it is important not to miss this diagnosis. However, only a few patients with  

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airflow limitation suffer from upper airway disease. Usually UAO is easily diagnosed when it occurs in an otherwise healthy subject, but it is often missed when present in patients with underlying lung diseases. In some of these cases neither clinical symptoms nor lung function tests suggest UAO. ROBERTSON et al [1] in a recent study have demonstrated that flow-volume curves do not help to differentiate between upper and lower airways obstruction in patients with an underlying obstructive bronchial disease. UAO must be suspected in patients with apparent resistance to bronchodilator and steroid therapy. For instance when an asthmatic shows poor response to high doses of steroids several complications should be suspected, such as steroid-resistant asthma, left ventricular failure, excessive anxiety and UAO.

Bronchiectasis is a disease characterized by a permanent dilation of the bronchial tree with chronic or intermittent bacterial colonization. Different abnormalities may be responsible for bronchiectasis such as immunodeficiency, cystic fibrosis, congenital anomalies, allergic broncopulmonary aspergillosis etc. Most of these patients, however, are idiopathic and only a few of them are hypogammaglobulinemic, thus they may benefit from a substitutive therapy which has proven to be a useful treatment in the prevention of bronchial infections [2]. On the other hand, steroids are indicated in the treatment of the typical eosinophilic pulmonary infiltrates of allergic broncopulmonary aspergillosis.

It has been suggested that progression of bronchiectasis results in a continuing "vicious circle". This hypothesis proposed by COLE [3] suggests that persistent bacterial colonization favours neutrophilic recruitment and liberation of excessive amounts of proteolytic enzymes which cause a persistent bronchial inflammation and progressive lung disease.

Much has been written with respect to the influence of bronchial infection in COPD, but in spite of this, the subject remains unclear. There is little evidence that exacerbations, whatever their cause and however they are treated, influence the long term course of airway obstruction in COPD patients. In contrast with COPD patients, antibiotics are indicated in bronchiectasis. Recent studies have demonstrated that prolonged (4 to 6 months) antibiotic treatment with higher than usually recommended doses may be a useful therapy in bronchiectasis [3].

Bronchial asthma is a complex disease in which an excessive release of mast cell chemical mediators seems to play a pivotal role. Mast cell stabilizers such as sodium cromoglycate and nedocromil sodium are specifically indicated in asthmatics especially in allergic young patients with intermitent asthma.

In addition to these specific treatments, the usual therapy for bronchial obstruction almost always includes bronchodilators and often steroids. These drugs are administered to obstructed patients independent of the etiology of the process responsible for the disease. This is because bronchial obstruction results in part from contraction of smooth bronchial muscle and inflammation.

A physician can treat his or her patients with three different bronchodilators: beta-adrenergic, anticholinergic and theophylline. Traditionally adrenergic agents have been considered the first choice bronchodilator treatment in bronchial asthma. However, recent studies have shown better results with a combination therapy including beta-adrenergics and anticholinergics than with single beta agents especially in the treatment of severe asthmatic exacerbations. Less consensus exists with respect to the appropriate bronchodilator therapy for emphysema and in general COPD patients. Although several studies have shown greater bronchodilator effect with anticholinergic drugs than with beta agents in these patients [4], other studies show equivalent effects. Independent of the results of these studies clinical experience shows that in general COPD patients usually prefer beta-agonists to anticholinergics.

Theophylline treatment can be used in all types of chronic obstructive lung diseases. Less agreement exists about the place of this drug in the management of bronchial obstruction. For some authors theophylline is a second-line drug in bronchial asthma and COPD patients because of its weak bronchodilator effect, frequent side-effects and difficult dosification. For other physicians however, its beneficial effects on smooth bronchial muscle, mucociliary clearance and respiratory muscle strength makes theophylline a first choice drug for obstructed patients [5]. During the last decade, many studies have been carried out to evaluate the therapeutic effects of a combined bronchodilator therapy including two or three drugs. In general these studies have shown that combined therapy either in COPD or asthmatic, is more efficient than treatment with a single drug.

Although no specific studies have been designed to evaluate combined or single bronchodilator therapy in bronchiectasis, it is reasonable to suspect that the results obtained in COPD patients can be extrapolated to bronchiectatic subjects.

According to the results of recent studies, five theoretical bronchodilator therapy strategies can be proposed to treat asthma while in the case of COPD, seven different strategies can be used (table 1). In the literature there are studies in favour of and opposed to all these possible treatments. The combination of bronchodilators with other treatment (steroids, sodium cromoglicate etc) complicates even more the number of possible options. I will deal later with all these possibilities.

Whatever its origin, immunological or not, inflammation is a constant phenomenon in airway obstruction. Steroid treatment, either by inhaled or by oral route, is usually prescribed to chronic asthmatics and its beneficial effects are beyond any doubt. The usefulness of steroids on COPD patients, however, is a matter of controversy. Some studies have demonstrated that steroids, may reduce bronchial inflammation. For instance, biochemical parameters such as collagenase activity or albumin secretion diminish with steroid treatment. Clinical studies on the short-term effect of corticosteroids, however, have yielded variable and conflicting results. Patients benefiting most from steroids seem to be those with a marrad improvement of
FEV₁, following inhalation of a bronchodilator drug, sputum or blood eosinophilia and those with wheezing as a predominant symptom. The therapeutic effect of steroids in COPD patients is usually evaluated by a short course of steroids [6]. It is conceivable, however, that the long-term benefit of steroids and other drugs such as bronchodilators in COPD patients may be related to airway inflammation changes which do not occur rapidly enough to be detected in short term studies. Obviously, a positive short steroid test suggests that steroid treatment may be a useful therapy, but a negative result does not negate the possible beneficial effect of a prolonged oral or inhaled steroid treatment. It is possible that such a treatment may prevent progressive airflow limitation or cause a slow but consistent reversion of bronchial obstruction. The approaches used to evaluate the efficacy of any treatment in bronchial asthma, a disease defined as reversible, cannot be directly extrapolated to the evaluation of COPD, a disease considered irreversible. New studies should assess the effect of treatment on quality of life and survival more than on their immediate bronchodilator action. To my knowledge only one survey has addressed this question. This study from Postma and coworkers [7] suggests that oral steroid in doses above 7.5 mg per day may slow down progression of the disease. Few studies have been carried out to evaluate the therapeutic effects of inhaled steroids in COPD patients. Again these studies have assessed beclomethasone on a short-term bases. As with oral steroids, a group of COPD subjects responded to beclomethasone treatment [8].

According to these findings it is not possible to deny the possible therapeutic benefit of steroid treatment based on a specific aetiologic diagnosis of airflow limitation. The design of a therapeutic strategy with bronchodilators and steroids is usually more conditioned by severity of the disease than by an accurate aetiologic diagnosis. Accordingly then, intermittent asthma should be treated with beta-adrenergics agents or a combination of beta₂ and anticholinergic drugs. Persistent asthma must be treated with prophylactic drugs such as sodium cromoglycate, nedocromil sodium and steroids. There is no doubt that in adults, inhaled steroids are better than mast cell stabilisers. A third alternative in persistent asthma is the association of beta₂ with theophylline and anticholinergics, but this treatment is usually less effective. Oral steroids are indicated in severe asthma with frequent exacerbations which do not respond to high doses of inhaled steroids (table 2).

It is more difficult to design a therapeutic approach in COPD patients than in asthmatics. This is due to a lack of information about the effects of inhaled steroids and oral steroids in these patients. It seems, however, that a combination of bronchodilator therapy with beta₂ and anticholinergics is better than single drug therapy. Although there are no studies on the effect of inhaled aerosols in COPD patients, there are arguments in favour of the use of these drugs in moderate COPD patients. Oral steroids are also indicated in the treatment of severe COPD patients with poor quality of life and frequent exacerbations. This decision should not necessarily be sustained by a positive short test with steroids.

Summarizing, a definite aetiologic diagnosis may have therapeutic implications in patients suffering from upper airway obstruction, bronchiectasis and bronchial asthma. Regarding bronchodilator therapy, a precise aetiologic diagnosis has few therapeutic implications. In mild asthma a beta-adrenergic or a combined therapy with beta₂ and anticholinergic drugs may be used. In mild COPD a combination therapy (beta₂ plus anticholinergic) is probably better than a single drug treatment. In persistent asthma, inhaled steroids are the first choice treatment, the use of additional single, double or triple bronchodilator treatment will depend on the results obtained by inhaled aerosol therapy. Oral steroids are indicated in patients who do not respond to high

### Table 1. - Bronchodilator therapy in asthma and COPD

<table>
<thead>
<tr>
<th>Option</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Beta-adrenergic</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td>2</td>
<td>Beta-adrenergic + anticholinergic</td>
<td>Beta-adrenergic + anticholinergic</td>
</tr>
<tr>
<td>3</td>
<td>Theophylline</td>
<td>Theophylline</td>
</tr>
<tr>
<td>4</td>
<td>Theophylline + anticholinergic</td>
<td>Anticholinergic + theophylline</td>
</tr>
<tr>
<td>5</td>
<td>Theophylline + anticholinergic + beta-adrenergic</td>
<td>Beta-adrenergic + theophylline</td>
</tr>
<tr>
<td>6</td>
<td>Theophylline + anticholinergic + beta-adrenergic</td>
<td>Anticholinergic + theophylline + beta-adrenergic</td>
</tr>
</tbody>
</table>

### Table 2. - Therapeutic strategies in bronchial asthma

<table>
<thead>
<tr>
<th>Mild Beta-adrenergic with or without anticholinergic</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st option (add) Inhaled steroids</td>
<td>2nd option Theophylline</td>
<td>4th option Mast cell stabilizer</td>
</tr>
<tr>
<td>3rd option Theophylline and inhaled steroids</td>
<td>Oral steroids</td>
<td></td>
</tr>
</tbody>
</table>

WIESBADEN SYMPOSIUM
doses of inhaled steroids. In moderate COPD patients, inhaled steroids and a combined bronchodilator therapy with two (β₂, plus anticholinergic) or three bronchodilators by adding theophylline is probably the best therapy. In severe COPD oral steroids should be added. Evaluation of the efficacy of all these treatments should be done on long-term basis.

References

Chronic wheezers. Treat and what the hell !

G.M. Cochrane*

Precise diagnostic labelling may be considered to be of the utmost importance by the academic, but the practising clinician knows such dogma may lead to less than ideal management of an individual patient. The precise diagnosis of emphysema, particularly non-obstructive emphysema, is increasingly recognised in pathology studies [1] and with CT scans [2] but the diagnosis by either technique may lead to an improvement in the individuals lifestyle but may also lead to a negative therapeutic approach by the doctor. The impression is that too precise a diagnosis in chronic wheezers may lead to withholding therapy which could be effective in an individual patient. Perhaps in the majority of people with diseases associated with airflow obstruction it is better to treat and assess response to treatment rather than to seek absolute diagnostic purity.

Misdiagnosis

Diagnostic labels in chronic airflow obstruction have already been extensively discussed but I consider them to be based on the “Dutch hypothesis”; that is, they are not separate diseases but a continuum of chronic disease and that they have in common the major risk factors of atopy and smoking which occur in about one third of the population. Misdiagnosis refers not to this continuum of disease but to the other diseases which may on initial presentation be confused because of their similar histories of wheeze, shortness of breath and sputum production (table 1). The diagnoses outlined in table 1 should be correctly made from a combination of taking the history, clinical examination and instigating appropriate investigation. Upper airway obstruction is associated with greater airflow obstruction during inspiration leading to stridor and the obvious abnormalities of the flow volume loop where there is a greater reduction in inspiratory flow rate during the forced vital capacity manoeuvre than in expiratory flow rates.

Table1. - Diagnoses not to be confused with chronic airflow obstruction

<table>
<thead>
<tr>
<th>Upper airway obstruction</th>
<th>Inhalation of a foreign body</th>
<th>Obstructing neoplasm</th>
<th>Pulmonary embolus</th>
<th>Cystic fibrosis</th>
<th>Pulmonary oedema</th>
</tr>
</thead>
</table>

The detection of an inhaled foreign body may be more problematic but the absence of generalised polyphonic wheezing in the presence of a unilateral monophonic wheeze is diagnostically helpful. Inhaled foreign bodies which are not radio-opaque may be demonstrated by taking chest radiographs in inspiration and expiration where in expiration the obstructed lung segment or lobe remains inflated while the remainder of the lung will deflate in a normal fashion. Obviously in this situation therapy is directed at the removal of the foreign body. Fortunately it is rare to confuse a neoplasm of the lung for a disease of chronic airflow obstruction even though...