Management of COPD and asthma in the 21st century

Newer therapies have improved the outlook for patients with both COPD and asthma.

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Exciting times lie ahead for pulmonologists. While the last decade belonged to the endocrinologists and rheumatologists, the vast array of new medications being introduced to the world of pulmonology bodes well for the health of our patients.

Airways diseases form the bulk of respiratory illnesses seen by pulmonologists, in particular chronic obstructive pulmonary disease (COPD) and asthma. The pathogenesis common to both these illnesses is inflammation. While it was initially thought that asthma was a disease of the larger airways, a significant body of research has refuted this long-held belief. We have now begun to understand that both COPD and asthma are inflammatory diseases that predominantly affect the small airways. Hence, new pulmonary drug development is aimed at either better drug delivery to the smaller airways or suppression of inflammation in the airways.

The new catch-phrase when choosing the appropriate therapeutic intervention in airway diseases is patient phenotyping. This alludes to subgroups of patients within these two disease entities, i.e. asthma and COPD, who have vastly different disease manifestations and responses to therapy.

Chronic obstructive pulmonary disease

In 2012, a major shift in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment recommendations was proposed. This new algorithm stratifies patients with COPD on the basis of symptoms and exacerbation history. Patients are now classified into groups A - D, using symptoms determined by the Modified Medical Research Council (MMRC) Dyspnea Scale or the COPD Assessment Test (CAT); and risk for exacerbation determined by FEV_1% predicted or prior history of exacerbations (Fig. 1).[1] The natural history of COPD is a disease characterised by repeated episodes of exacerbation of symptoms. It was assumed that these exacerbations were random events in the course of the disease. Current evidence suggests that this is not the case as these exacerbations clump together, implying that the first exacerbation significantly increases the risk of a second exacerbation. Exacerbations are a significant cause of morbidity and mortality in COPD and are associated with more rapid disease progression and poor quality of life.[2] With this in mind the main goals of COPD management are to reduce symptoms and prevent exacerbations.

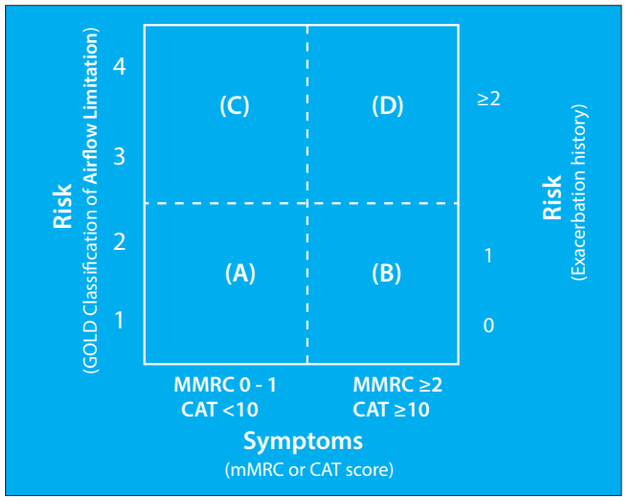

Fig. 1. New COPD classification (MMRC = Modified Medical Research Council; CAT = COPD Assessment Test).

Exacerbations are a significant cause of morbidity and mortality in COPD and are associated with more rapid disease progression and poor quality of life.

Symptom control

Symptom control is achieved predominantly by improving airflow limitation and reducing dynamic hyperinflation. Airflow limitation is mainly treated with bronchodilators. A vast array of new bronchodilator drugs are currently being developed or in phase three clinical trials. They fall into two categories i.e. the β_2 agonists and muscarinic receptor antagonists. The latest drugs available in the β_2 category are the longer-acting β_2 agonists – the ultra-LABAs – and include indacaterol, carmoterol, vilanterol and olodaterol. All of the ultra-LABAs have a duration of action greater than 24 hours and are suitable for once-daily dosing. Also, some of the newer long-acting antimuscarinic agents (LAMAs) include drugs such as aclidinium and glycopyrrolate.[3] The UPLIFT and INSPIRE trials were landmark trials that demonstrated the benefits of tiotropium therapy in patients with COPD. Patients receiving tiotropium had significant improvement in lung function and health-related quality of life and had a reduced risk of exacerbations, episodes of respiratory failure, and hospitalisation due to COPD exacerbations. In addition, it has now been shown that treatment with tiotropium over 4 years is associated with decreased mortality.[4] Indacaterol, the latest LABA, was demonstrated to be at least as effective as tiotropium in improving trough FEV_1, dyspnoea, and quality of life, with similar trends in reduction of exacerbations in patients with COPD.[5]

Management of exacerbations

Management of exacerbation-prone COPD patients mandates the administration of the influenza and pneumococcal vaccinations. Specific therapy for the reduction of exacerbations includes the addition of a phosphodiesterase-4 inhibitor, roflumilast. It has recently been registered in South Africa for the treatment of severe COPD associated with chronic bronchitis and a history

of frequent exacerbations.[6] A major side-effect of the drug is diarrhoea, which may precipitate weight loss. Albert *et al.*[7] also showed that, in COPD patients with an increased risk of exacerbations, the addition of azithromycin (250 mg daily for 1 year) as well as their usual care, reduced the frequency of exacerbations and improved quality of life. Unfortunately, it also caused hearing loss in a small percentage of subjects. Furthermore, the potential effects of long-term treatment with azithromycin on microbial resistance patterns as well as its cardiovascular safety profile are unknown. Currently, macrolide therapy seems effective in decreasing the frequency of exacerbations in patients with COPD, but this benefit is only observed when used for more than 6 months. More worrying of late has been the association with the use of fixed-dose inhaled corticosteroids (ICS) plus LABA combinations and the incidence of pneumonia in patients with COPD. With the publication of the PATHOS trial data some of these fears have been alleviated. The PATHOS data concluded that long-term treatment with fixed-combination budesonide/formoterol was associated with fewer healthcare utilisation-defined exacerbations than fluticasone/salmeterol and a lower incidence of pneumonia in patients with moderate and severe COPD.[8] A recent randomised placebo-controlled trial shows the benefit of N-acetylcysteine (NAC) at a dose of 600 mg twice daily. Patients followed up after 1 year had better measures of airway reactance, and resistance improved significantly in the NAC group but not in the placebo group. COPD exacerbations occurred less often with NAC than with placebo.[9] Most importantly, a Swiss study published in June 2013 in *JAMA*[10] demonstrated that even in hospitalised COPD patients with severe or very severe baseline disease, a 5-day course of oral prednisone 40 mg daily was as effective as a 9-day course.

Ancillary medication

Ancillary medication used in the management of patients with COPD includes theophylline and nortryptaline. Their major function is not bronchodilation but rather restoring steroid sensitivity. It is thought that these drugs improve steroid sensitivity by selective activation of histone deacetylase (HDAC) activity, in particular HDAC2, which suppresses inflammation in COPD. Gene expression is regulated by acetylation of core histones by histone acetyl transferases (HAT), which open up the chromatin structure (chromatin remodelling) to allow gene transcription. HAT activity in COPD is reversed by HDACs, which in turn are activated by theophylline and nortryptaline.[11]

Rehabilitation and prognosis

Of all therapies for COPD, few are known to influence survival. In a select group of patients, however, oxygen is one of those therapies. Long-term domiciliary oxygen therapy (LDOTS) in appropriately selected patients improves exercise capacities and dynamic hyperinflation, and thus has an impact on mortality in those with advanced COPD. Finally, one of the few surgical therapies demonstrated to improve survival in COPD is lung volume reduction surgery (LVRS). It is believed that these benefits result from improvement in respiratory mechanics, but LVRS also results in a decrease in inflammatory mediators including C-reactive protein, TNFα, interleukin (IL)-6, and IL-8 and an increase in α_1-antitrypsin and body mass index. Elimination of inflammatory tissue may contribute to these findings; alternatively, surgically induced anatomical changes could result in a reduction in systemic inflammation, which is a novel concept in COPD.[12]

Pulmonary rehabilitation is an important therapeutic intervention in COPD patients. The negative interaction between the respiratory, cardiovascular, and musculoskeletal systems in patients with COPD plays a significant role in exercise limitation (Fig. 2). Therefore, regular follow-up at a dedicated pulmonary rehabilitation clinic with experienced physiotherapists significantly improves outcomes in patients with severe COPD. One of the most important aspects of the rehabilitation process is smoking cessation assistance. This includes pharmacological and non-pharmacological means to aid patients in smoking cessation and remaining free of the habit.

Asthma

For the management of patients with asthma, the goals are slightly different. Previously, therapeutic interventions were chosen and titrated by the severity of the initial presentation. However, asthma is a heterogeneous condition characterised by frequent acute episodic exacerbations. These

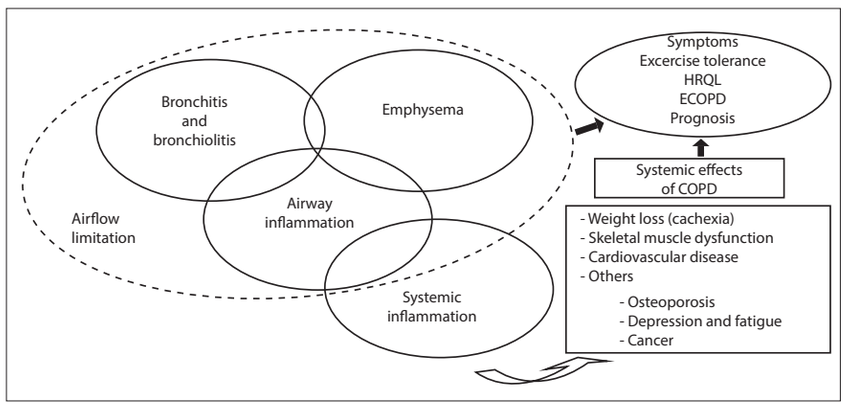

Fig. 2. Systemic manifestations of COPD (HRQL = health-related quality of life; ECOPD = exacerbation of COPD).

exacerbations occur against a background of chronic persistent inflammation and structural changes that result in persistent symptoms and reduced lung function.[13] These frequent exacerbations have led to a change in the goal of asthma therapy to one of achieving 'total asthma control'.[14-16] Hence, based on the exacerbation rates, two asthma phenotypes have been described.[17] This distinction has been made on the basis of the presence or absence of tissue eosinophils. Patients with asthma who have airway eosinophilia have greater airway remodelling and more exacerbations, whereas those without eosinophilia have more airway obstruction.[18] Subsequently, numerous studies support the idea that, although many patients with asthma do not have any eosinophilic inflammation, the presence of such inflammation identifies a more exacerbation-prone phenotype.[19] Initially, practice guidelines for asthma treatment aimed to minimise symptoms, optimise lung function, and prevent exacerbations.[19] While referring to this aim, lung function was frequently the primary endpoint. With the subsequent recognition of the importance of the patient perspective, and the poor correlation between lung function, airway inflammation and symptoms, therapeutic interventions have increasingly focused on the assessment of 'asthma control'.[21] Asthma control is therefore a summary term implying a global assessment of symptoms, reliever use, lung function, and frequency of exacerbations and can be numerically quantified with either the Asthma Control Test or the Asthma Control Questionnaire.[9,13]

A vast array of new bronchodilator drugs are currently being developed or in phase three clinical trials.

Control

Asthma control is defined as the extent to which the various manifestations of asthma have been reduced or removed by treatment. This includes two components: firstly, the level of clinical control (i.e. day-to-day control) gauged from features such as symptoms and the performance of activities of daily living; and secondly, minimising the risk of future adverse events, including loss of control, exacerbations and accelerated decline in lung function.[13,22] While the goal standard therapy for asthma still remains ICS plus LABA combination inhaler therapy, the identification of the molecular processes driving the airway inflammation has led to the development of a multitude of new therapies. These include omalizumab (an anti-IgE antibody), mepolizumab (an anti-IL5 monoclonal antibody), lebrikizumab (an IL-13 antibody) and the most recently studied subcutaneously administered dupilumab (an antibody to the alpha subunit of the IL-4 receptor), which inhibits signalling by both IL-4 and IL-13.[23] All of these newer therapies are reserved for patients with refractory symptoms and persistent airway inflammation. However, this group form the minority of patients with asthma. For the vast majority of patients, the ICS plus LABA combination, with the addition of either a leukotriene receptor antagonist (i.e. montelukast) or a LAMA (i.e. tiotropium), will provide adequate control.[24] Furthermore, triple therapy with ICS plus LABA plus LAMA combination therapy improves lung function and decreases asthma exacerbations.[25]

Ancillary treatment

The addition of a proton pump inhibitor (PPI) to optimal inhaler therapy is controversial. The publication of the SARA study has provided some guidelines, concluding that asymptomatic gastro-oesophageal reflux disease (GORD), although present in many patients with uncontrolled moderate to severe asthma, is not associated with poorer asthma control, and therefore treatment of this entity does not improve control. Furthermore, the authors concluded that, given the cost of PPIs and the increased incidence of community-acquired pneumonia and *Clostridium difficile* infections in patients on long-term PPIs, it seems reasonable to reconsider and appropriately evaluate this treatment option in patients with symptoms of GORD. However, the SARA study does not support this approach in those without symptoms.[26-28] Supplemental vitamin D in patients with asthma holds some promise with regard to immunomodulation and its effects on T_0/Treg signalling. Unfortunately, we have to await the outcome of the ongoing the NHLBI's AsthmaNet investigator's trial to provide clear guidelines regarding vitamin D supplementation and asthma.[29,30] There has also been considerable interest in the use of antibiotics as immunomodulators in asthma. Thus far, the macrolide antibiotic group has been the most extensively studied. The conclusion of the most recent Study of Macrolides in Asthma Trial stated that the addition of clarithromycin to fluticasone in adults with mild-to-moderate persistent asthma sub-optimally controlled by low-dose ICS alone, did not further improve asthma control. Although there was an improvement in airway hyper-responsiveness with clarithromycin, this benefit was not accompanied by improvements in other secondary outcomes, i.e. FEV_1.[31] A recent meta-analysis in July 2013 concluded the following: macrolide administration for asthma for 3 or more weeks was not associated with improvement in FEV_1, but produced significant improvements in peak expiratory flow, symptoms, quality of life, and airway hyper-reactivity. Macrolides may therefore be beneficial as adjunctive asthma therapy. Future trials, focusing on long-term safety and effectiveness, should provide guidelines for the use of macrolides in patients with asthma.[32]

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Finally, for refractory severe asthma, bronchial thermoplasty now seems to offer significant benefit. Bronchial thermoplasty is a bronchoscopic procedure approved for the treatment of severe asthma. In non-obese patients with adult-onset non-eosinophilic severe asthma, this might be one of the only effective therapeutic options. During this procedure, controlled thermal energy is applied to the airway wall to decrease the amount of smooth muscle, and the response is sustained at follow-up after 1 year.[33]

Therefore, as mentioned in the introduction, the future for pulmonologists and more importantly our patients is ... A BREATH OF FRESH AIR.

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Summary

- Asthma and COPD are inflammatory airways diseases with significant systemic effects.
- Appropriate therapeutic intervention in airway diseases depends on patient phenotyping.
- New GOLD treatment recommendations stratify patients with COPD on the basis of symptoms and exacerbation history.
- The main therapies available to address airflow limitation are bronchodilators, of which there are two categories – β_2 agonists (LABA) and muscarinic receptor antagonists (LAMA).
- Management of exacerbation-prone patients with COPD includes vaccinations, addition of a phosphodiesterase-4 inhibitor, roflumilast and daily azithromycin and NAC.
- Budesonide/formoterol was associated with fewer healthcare utilisation-defined exacerbations than fluticasone/salmeterol and a lower incidence of pneumonia in patients with moderate and severe COPD.
- Pulmonary rehabilitation and smoking cessation assistance forms the backbone of supportive therapy.
- Asthma is characterised by frequent acute episodic exacerbations against a background of chronic persistent inflammation and structural changes which result in persistent symptoms and reduced lung function.
- Current goals of asthma therapy are to achieve 'total asthma control'.
- Newer therapies in asthma include omalizumab (an anti-IgE antibody), mepolizumab (an anti-IL5 monoclonal antibody), lebrikizumab (an IL-13 antibody) and the most recently studied dupilumab (a subcutaneously administered antibody to the alpha subunit of the IL-4 receptor which inhibits signalling by both IL-4 and IL-13).
- Asymptomatic GORD, although present in many patients with uncontrolled moderate to severe asthma, is not associated with poorer asthma control, and therefore treatment of this entity does not improve control.
- Macrolides may be beneficial as adjunctive asthma therapy.