

Pulmonary and Critical Care Updates

Update in Chronic Obstructive Pulmonary Disease 2009

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The year of 2009 has turned out to be a fruitful year in terms of scientific publications in the field of Chronic Obstructive Pulmonary Disease (COPD). As reviewed below, these publications helped us to better understand the natural history of this devastating disease, to better phenotype patients, to validate new composite outcomes and, which is even more important for our patients, to demonstrate that by treating patients adequately, they live longer and better. All of this has been accompanied by further evidence supporting the importance of comorbidities in the whole complexity of our patients, and by new data that points to the immune system as a key player in the development of COPD. Finally, during the year of 2009, we had to deal with an outbreak of a pandemic influenza A (H1N1) virus, in which COPD was one of the frequent underlying medical conditions facilitating the development of severe respiratory failure.

NATURAL HISTORY

Understanding lung development and aging, both in health and disease, as well as the gender differences associated with them, is essential for setting priorities and targets when monitoring and treating lung diseases. The Fletcher and Peto (1) lung function curves have been used as a reference since their publication back in the seventies. This year, a prospective study of the Framingham Offspring cohort revisited them with a larger population of males and for the first time, females, which was followed up for 23 years, from adolescence to old age. The main novel observations of this study were that: (1) the normal rate of lung function decline in healthy never-smokers, both in males and females, is smaller (~20 ml/yr) than previously thought (~30 ml/yr); (2) the deleterious effect of smoking cigarettes on the rate of lung function decline is similar in both sexes; (3) the presence of respiratory symptoms identifies a population of smokers particularly susceptible to the development of airflow limitation; and (4) the benefit of quitting smoking is more pronounced when quitting earlier (2, 3). It is now easier to understand the data reported in the Rotterdam Study that addresses the important issue of a remarkably high incidence of COPD in the youngest women, which suggests a further shift toward females in the sex distribution of COPD (4). Importantly, despite this potential change in incidence, mortality remains higher in males than females, even in well-matched BODE [body mass index, airway obstruction, dyspnea, and exercise capacity] patients (5).

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GENETIC SUSCEPTIBILITY

The search for the Holy Grail of identifying genes that increase the susceptibility of smokers to develop COPD is still not resolved. A meta-analysis on 20 polymorphisms in 12 candidate genes involved in the protease–antiprotease balance and several antioxidant pathways showed that, after combining independent studies, many candidate genes had no association with COPD (6). It also showed that the choice of populations for a meta-analysis study strongly affects the final results, as some of the associations have opposite effects in certain ethnic groups (6). Another attempt to link genes with the risk of developing COPD, involving polymorphisms of the C-reactive protein (CRP) gene, has also proved unsuccessful (7).

PATHOGENESIS

COPD is a chronic inflammatory disease of the lungs that progresses slowly. The majority of patients are therefore elderly. There is increasing evidence for a close relationship between aging and chronic inflammatory diseases leading to the hypothesis that accelerating aging of the lung in response to oxidative stress might be involved in the pathogenesis and progression of COPD, particularly emphysema (8). This results from a failure of organs to repair DNA damage by oxidative stress (nonprogrammed aging) and from telomere shortening as a result of cell division (programmed aging). Telomere length is indeed considered a marker for biological aging, and excess telomere shortening is consistently found in COPD (9, 10). Another condition that manifests clinical features consistent with accelerated aging is Werner's syndrome. Cigarette smoke induces cellular senescence via Werner's syndrome protein down-regulation in lung fibroblast, which suggests that this pathway may be involved in smoking-related diseases and may eventually constitute a novel therapeutic target (11). Defective repair has been also related to aging. In this context, several pathways can influence this process including a dysregulation of the Smad pathway in response to cigarette smoke exposure (that results in an impaired extracellular matrix repair) (12), a down-regulation of the Notch pathway (that controls epithelial differentiation in lung morphogenesis and is associated with smoking and COPD) (13), and the dysregulation of apoptotic cell clearance through oxidant-activation of the RhoA-Rho kinase pathway in the presence of cigarette smoke (14). Disruption of growth factor signaling cascades critical for lung development and postnatal homeostasis may also promote the development of emphysema in response to cigarette smoke. This could be the case for neuropilin-1—an integral component of receptor complexes mediating alveolar septation and vascular development—that is dysregulated in response to cigarette smoke-enhancing apoptosis of type I and type II epithelial cells and airspace enlargement (15).

Excessive mucin production is another characteristic of advanced COPD. Local pharmacological inhibition of matrix metalloproteinase 14, a major proteinase involved in mucin

expression, has been shown to be useful in reducing cigarette smoke–derived acrolein-induced mucin levels in mouse lungs (16).

An intriguing hypothesis suggesting a role for autoimmunity in the pathogenesis of COPD has emerged in the past few years and is maturing rapidly (17). It proposes that the immune mechanisms that lead to COPD follow three steps (18). The first one is characterized by an innate immune response to cigarette smoke that relies on the recognition of tissue damage by Toll-like receptors (19) and is driven by epithelial cells, macrophages, and neutrophils. The second step involves T cell activation and proliferation (20), as well as maturation of dendritic cells known to increase in the lungs of patients as COPD progresses (21). The third and final step would be an adaptive immune reaction driven by CD8⁺ cytotoxic T cells, Th1 T cells, and oligoclonal B cells, all of which are found in patients with severe COPD (22). These cells express the chemokine receptor CXCR3 and its ligands, which contribute to lymphoid follicles formation (23). This latter step would contribute to the persistence of the inflammatory response years after the cessation of smoking in response to self-antigens produced all along this process, a feature of autoimmune diseases (18). Further research is, however, required to demonstrate the cause–effect relationship between autoimmunity and the development of COPD. Finally, other effects of cigarette smoke, such as the skewedness of the immune responses to promote infection and lung cancer (24), as well as a potential effect on COPD exacerbations (25), will have to be taken into account to have a complete picture of COPD pathogenesis.

ASSESSMENT OF PATIENTS

Because COPD is increasingly recognized as a multi-component disease with systemic consequences, it is increasingly accepted that the degree of airflow obstruction determined by the FEV₁, so far the most common parameter to classify and monitor the disease, provides limited reflection of how the different domains of the disease affects patient's life. By contrast, composite indices take into account different aspects of the disease. The first important attempt in this context was the BODE index that, by combining the body-mass index (BMI), airflow limitation (FEV₁), symptoms (as measured by the MRC scale) and exercise capacity (6-min walking distance [6MWT]), predicts mortality in COPD better than lung function alone (26). However, the BODE index is not widely used in clinical practice because 6MWT is time consuming, requires supervision and space, and has not been calibrated to accurately predict the absolute risk of an event in individual patients. This year, an updated BODE index with a simplified point system has been calibrated to predict absolute risks, and a simplified index, the ADO index, has been developed (27). The ADO index includes age, dyspnea, and airflow obstruction and does not require 6MWT, which may facilitate its use in primary care settings. The DOSE index, another attempt to create a multicomponent assessment index of COPD severity, includes symptoms (MRC dyspnea scale), airflow limitation (FEV₁), smoking status (current vs. former) and, importantly, previous exacerbation frequency (28). Unlike other severity indices, the DOSE index aims at being used in routine clinical practice in all stages of disease severity.

A different aspect that can potentially be added to the routine clinical evaluation of patients with COPD is to obtain, from the patient, reliable and valid information on the impact of COPD on their health status. Current health-related quality of life questionnaires provide valid assessment of COPD but are complex and not useful in clinical practice. For these reasons, a short and reliable instrument, the COPD Assessment Test

(CAT), has been developed and validated (29). It includes eight different domains (cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy) and, although it needs to be validated in different countries and languages, the CAT questionnaire may greatly facilitate the communication between the clinician and the patient, enabling a common understanding of the severity and impact of the disease.

COMORBIDITIES

As a multi-component disease, COPD is frequently associated with different organs/systems dysfunction. Of particular interest is its association with increased morbidity and mortality from cardiovascular disease (30). Smoking is an established risk factor for both COPD and cardiovascular diseases, and low-grade systemic inflammation, as measured by CRP, has been suggested to link both diseases through increased atherosclerosis (31). This association is even more pronounced during exacerbations of COPD, where high CRP appears to increase the risk of myocardial infarction and stroke (32). This year, new data showed that smokers with airflow limitation have exaggerated subclinical atherosclerosis (33). Moreover, middle-aged men who are susceptible to COPD may also be susceptible to vascular atherosclerosis, and atherosclerotic changes may start early in the disease process of COPD (33). Atherosclerosis is also associated with vascular dysfunction and arterial stiffness, and recently COPD has also been associated with increased arterial stiffness, although not with impairment of endothelial vasomotor or fibrinolytic function in comparison with age-matched control subjects with similar cigarette smoke exposure (34).

Data from the TORCH (Toward a Revolution in COPD Health) study (30) confirmed previous observations regarding the high prevalence of osteoporosis in patients with COPD, irrespective of sex. Yet, a study in a subset of patients within this randomized, double-blinded, placebo-controlled study, found no evidence of a significant effect of inhaled corticosteroid therapy (compared with placebo) on bone mineral density and bone fractures (35). A daily dose of 700 to 800 IU of vitamin D, combined with adequate daily calcium intake (1,000 mg) is probably the best strategy to prevent fractures in postmenopausal women and/or older men (≥50 yr), specifically those with a risk of hip fracture (36). However, the effects of vitamin D therapy may go beyond the bones as it also down-regulates the inflammatory immune response in the airways, boosts innate immune defenses against different microorganisms, and there is evidence to suggest that it may interfere with other comorbidities of COPD such as skeletal muscle weakness, cardiovascular disease, and cancer (37).

Another frequent, but often overlooked comorbidity of COPD is depression. New evidence suggests that depressive symptoms assessed in stable patients with COPD are associated with all-cause mortality (38). Alzheimer disease and vascular dementia could also be related, or at least, exacerbated by COPD, as it has been shown that COPD increases the risk of cognitive decline among older adults surveyed in a large, population-based longitudinal cohort (39). A condition that is associated with cognitive decline and frequently overlaps with COPD is obstructive sleep apnea. Due to their elevated prevalence, these two respiratory disorders often coexist (overlap syndrome) but a study this year suggests that both conditions may also share some common pathophysiology, in particular, in relation to systemic inflammation and cardiovascular disease (40).

Finally, another condition that often coexists and shares a common risk factor with COPD is lung cancer (41). An alternative view to common risk factor is that COPD is independently and closely related to lung cancer and that these

diseases even share underlying host-susceptibility factors. To address some of these issues, in particular, to ascertain the prevalence of COPD in recently diagnosed lung cancer cases, to determine the effect of the cancer on spirometry, and to establish the degree to which COPD is more often found in lung cancer cases than in appropriately matched controls, a cross-sectional study randomly recruited participants from the community and concluded that COPD is both a common and important independent risk factor for lung cancer (42).

EXACERBATIONS

The natural history of COPD is characterized by the repeated occurrence of episodes of exacerbation of symptoms (43). It is assumed that exacerbations are random events in the course of the disease. Yet, recent evidence suggests that this is not the case, insofar as exacerbations cluster together in time, implying that after a first exacerbation, patients are at increased risk of a second exacerbation (44). This finding has important implications for the design of preventative interventions and the analysis of exacerbations data in clinical trials.

Although the pathogenesis of exacerbations is not entirely clear, viral and bacterial infections appear to trigger most cases (43). Interestingly, during the spring of 2009 we faced a pandemic of influenza A (H1N1) virus that caused severe illness especially to patients with underlying medical conditions. Unexpectedly, however, the analysis of hospitalized patients in the United States between April and mid-June 2009 revealed that asthma (28%) was more frequently associated with severe H1N1 infection than COPD (8%) (45). Other noninfectious triggers may also play a role in the pathogenesis of exacerbations. A recent study suggested that an abnormal coordination of swallowing and breathing can promote prandial aspiration and trigger exacerbations (46). Abnormal swallowing reflexes in COPD might also be affected by the frequent occurrence of gastro-esophageal reflux disease that can favor bacterial colonization and predispose to frequent exacerbations (47). Likewise, defective macrophage phagocytosis of bacteria in COPD may facilitate airway bacterial colonization and promote exacerbation frequency (48). This abnormality may also influence the underlying inflammatory response because bacterial colonization, in particular by nontypable *Haemophilus influenzae* (NTHi), is associated with increased inflammation (49, 50). Interestingly, cigarette smoke exacerbates the inflammatory response to NTHi via skewed inflammatory mediator expression (25).

There is a clear need to identify biomarkers that can help clinicians predict and diagnose better exacerbations. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study is beginning to provide interesting results in this setting. Hence, the serum surfactant protein D (SP-D), a lung-derived protein, may be useful in identifying individuals who are at increased risk of exacerbations of COPD and, what is relevant for monitoring the response to treatment, it is steroid sensitive (51). Other markers, such as the serum IP-10, have also been shown to increase during exacerbation of COPD due to human rhinovirus infection (52).

MANAGEMENT AND PREVENTION

The main goals of COPD management are to reduce symptoms and mortality and to prevent exacerbations (53). Prevention strategies with influenzae and pneumococcal vaccination are recommended (53), although recent data suggest that influenza but not pneumococcal vaccination is associated with a reduced risk of all-cause mortality in COPD (54). New pneumococcal vaccination in patients with COPD, such as the new 7-valent

diphtheria-conjugated pneumococcal polysaccharide vaccine, seems to induce a superior immune response than the 23-valent pneumococcal polysaccharide vaccine currently used (55).

During this year we witnessed important results from large randomized controlled trials on pharmacological intervention in COPD. The original results from the TORCH study supported a borderline benefit in patients receiving the combination of inhaled fluticasone and salmeterol on mortality (30). Further evidence of beneficial effect on mortality is now presented in the analysis of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study (56), a 4-year trial of tiotropium treatment on top of usual care that included a combination of inhaled glucocorticoids and a long-acting β -agonist (LABA) in more than 60% of patients. The UPLIFT trial showed no effect on the main outcome—the rate of decline of FEV₁ over placebo—but, at all time points, patients receiving tiotropium had significant improvements in lung function and health-related quality of life and had a reduced risk of exacerbations, episodes of respiratory failure, and hospitalization due to COPD exacerbations when compared with placebos (57). In addition, it has now been shown that treatment with tiotropium over 4 years is associated with decreased mortality, with this effect being more prominent in the cardiac and respiratory systems (56). Another important effect of tiotropium emerged from the analysis of the subgroup of patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) Stage II disease at randomization in the UPLIFT, which included 2,739 participants. In this subgroup of patients, treatment with tiotropium was associated with a lower rate of decline in mean post-bronchodilator FEV₁, better health status, and longer time to first exacerbation compared with placebo (58). A post-hoc analysis of TORCH also found that, compared with placebo, treatment with fluticasone/salmeterol may also reduce mortality in patients with GOLD Stage II disease, reduce exacerbations, and improve health status (59). These findings suggest that early pharmacological intervention in COPD is relevant to COPD management. Finally, tiotropium has been shown to protect from dynamic hyperinflation independently of the extent of emphysema (60, 61). Dynamic hyperinflation is associated with a reduced daily physical activity in these patients (62), which leads to more exacerbations and mortality (63) and could explain some of the effects described.

Because most patients in UPLIFT were receiving inhaled corticosteroids (ICS)/LABA, debate remains concerning the benefit of the triple association of those with tiotropium. A recent study has shown that budesonide/formoterol added to tiotropium, compared with tiotropium alone, improved overall lung function, daytime and nighttime symptoms, and reduced severe exacerbations in patients eligible for ICS/LABA therapy (64), which confirms previous observations (65).

There is concern about an increasing risk of pneumonia in patients with COPD who use inhaled corticosteroids (66). An article by Crim and colleagues analyzed data from TORCH and identified specific risk factors for the development of pneumonia in patients with COPD who received inhaled steroids (67). This included advanced age, severe airflow limitation, and a history of previous exacerbations (67). Yet, a recent meta-analysis of individual patient data found that budesonide treatment does not increase the risk of pneumonia in patients with COPD, although studies included in this meta-analysis were of relatively short duration (12 mo) (68).

The relatively poor response of airway inflammation to steroids in patients with COPD has been related to a decreased histone deacetylase activity (69, 70). Nevertheless, some recent data on the effects of steroids reducing vascular remodeling in these patients challenges this view (71). Therefore, predicting corticosteroid response would be of interest, although attempts

to use exhaled nitric oxide to this end have proved disappointing (72). Still, corticosteroids might exert their antiinflammatory properties more effectively if histone deacetylase activity is boosted with low-dose theophylline (73) or by inhibition of phosphoinositol-3-kinase (PI3K) (74).

Roflumilast, a phospho-diesterase-4 inhibitor, has shown efficacy and acceptable tolerability in preclinical and clinical studies in patients with COPD (75). In two randomized trials in symptomatic patients with severe COPD and a history of exacerbations, roflumilast was shown to significantly improve both lung function and the frequency of exacerbations after 1 year, independent of the patient's smoking status or use of concomitant medication (76). The effect on lung function was further confirmed in two different trials in which roflumilast or placebo was added to salmeterol or tiotropium, although with expected class-specific adverse events in nearly 15% of patients treated with roflumilast (77). Of particular concern is weight loss, a side-effect that deserves further investigation in patients receiving roflumilast.

A novel approach has been proposed that addresses inflammation in COPD with low-dose macrolides (clarithromycin and erythromycin). A randomized, double-blind, placebo-controlled study of 250 mg erythromycin administered twice daily to patients with COPD over 12 months showed a significant reduction in exacerbations when compared with placebo (78). Recent evidence suggests that clarithromycin prevents emphysema evoked by cigarette smoke by modulating lung inflammation in mice, which could provide a new therapeutic strategy for COPD (79).

Nonpharmacological management of COPD has also been updated with a new analysis of patients undergoing lung-volume reduction surgery in the National Emphysema Treatment Trial. This treatment aims to reduce lung hyperinflation and improves survival in some patients with advanced emphysema (80). New evidence demonstrates a beneficial effect on a composite endpoint consisting of the occurrence of death or a clinically meaningful decline in quality of life, which indicates a significant palliative effect beyond the survival benefit (81). A different option for lung-volume reduction, a novel endobronchial treatment for advanced emphysema that reduces lung volume by instillation of a fibrinogen biopharmaceutical suspension and thrombin solution that polymerize *in situ* to form a hydrogel, has shown functional improvement and an acceptable security profile (82). An interesting approach to reduce the effects of dynamic hyperinflation and increase exercise tolerance has been provided by a study showing that breathing normoxic heliox (mixture of 79% helium and 21% oxygen) increases lower limb oxygen delivery and use in patients with moderate to severe COPD (83). An alternative view is to improve muscle contractility with the calcium sensitizer, levosimendan, which has been shown to improve contractile muscle protein function in diaphragm muscle fibers of patients with COPD (84).

Although we are far from understanding the whole complexity of this devastating disease, important achievements have occurred over the last few years to increase our knowledge for providing better treatment for these patients, making the future look promising. During 2009, we witnessed important gains in understanding the natural history of the disease as well as in assessing patients. Also, progress has been made to improve our knowledge of the key events that led to the development of COPD. Furthermore, we found that treating patients early in the natural history of the disease is meaningful, and that new therapeutic approaches and drugs are in the pipeline that will hopefully result in better health for our patients.

Conflict of Interest Statement: B.G.C. has received advisory board fees from Novartis and AstraZeneca (both for \$1,001–\$5,000); he has received lecture fees (all for

nonpromotional CME activities) from GlaxoSmithKline, Boehringer Ingelheim, and AstraZeneca (all up to \$1,000). A.A. has received advisory board fees from GlaxoSmithKline, Almirall, and Altana (all for \$5,001–\$10,000); he has received lecture fees from GlaxoSmithKline, AstraZeneca, and Almirall (all for \$5,001–\$10,000); he has received industry-sponsored grants from GlaxoSmithKline (more than \$100,001), AstraZeneca, Pfizer (\$10,001–\$50,000), Boehringer Ingelheim (\$5,001–\$10,000), and Almirall (more than \$100,000).

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