

EDUCATIONAL ARTICLES

What's new in COPD?

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is now established as one of the most prevalent causes of morbidity and mortality in our time and its incidence is increasing. Once airflow limitation is present it is usually progressive and the associated inflammation has both pulmonary and systemic sequelae.¹ COPD research in recent years has focused on several key areas, including disease definition, biomarkers of inflammation, oxidative stress and proteolytic balance, prognostic indicators and therapeutic validation. This review will highlight key areas of research in COPD and assess whether progress is being made in the definition, pathogenesis and management of this important condition.

Definition and Diagnosis

COPD is now generally defined as a fixed obstructive ventilation defect (post-bronchodilator Forced Expiratory Volume In One Second (FEV_1) <80% predicted, FEV_1 /Forced Virtual Capacity (FVC) ratio <70%) which is not fully reversible with bronchodilators. Some ambiguity persists in both the definition of fixed airflow limitation, particularly over the use of a fixed FEV_1 /FVC ratio <70% which leads to over diagnosis of COPD particularly in the elderly. In addition American Respiratory Society (ATS),² European Respiratory Society (ERS),¹ British Thoracic Society (BTS)³ and National Institute of Clinical Excellence (NICE) guidelines differ slightly in their definitions of disease severity, the need for reversibility testing and on whether values are taken pre- or post-bronchodilator (Table 1). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) initiative and the ERS /ATS guidelines link severity based on the FEV_1 with guidance on treatment, whereas the NICE guidelines base treatment on the presence of symptoms with COPD severity.

Table 1 Defining COPD Severity and Guidance for Treatment Using FEV1 (in the presence of an $FEV_1/FVC <0.7$)

| Guidelines | Mild | Moderate | Severe | Very severe |
|--------------|--|---|-----------------------------|---|
| ERS/ ATS | ≥80% | 50-79% | 30-49% | ≤30% |
| BTS and NICE | 50-80% | 30-49% | <30% | |
| GOLD | ≥ 80% | 50 79% | 30 - 49 | ≤ 30% OR < 50% + chronic respiratory failure |
| Treatment | Smoking cessation, Influenza vaccination, Short acting bronchodilators | Add regular long acting bronchodilators, Pulmonary rehabilitation | Add inhaled glucocorticoids | Add long term oxygen if chronic respiratory failure, consider surgery |

Health economics and service planning for COPD have been hindered by inaccurate recording on medical records and death certificates. Despite international consensus on COPD as a unifying title, there remain more than four ICD-10 classifications for airways obstruction. There was an increase in the recording of COPD as the main cause of death from in 3.4% in 1977 to 6.1% in 2001 in a Danish study,⁴ but COPD is still under-diagnosed. In a survey of those with spirometry criteria for COPD only 18.8% had any respiratory diagnosis. Even in those with spirometry indicative of severe or very severe COPD, only 46.8% had any respiratory diagnosis.⁵ The Copenhagen City Lung Study found that for patients with mild, moderate and even severe disease, COPD was often not recorded on the death certificate (only 24.9% of patients with at least severe COPD had it mentioned on the certificate at death). In some cases COPD was recorded as a cause of death when on reviewing the notes, this diagnosis seemed unlikely.⁶ Compared to lung cancer and asthma, the term COPD is still relatively unfamiliar to the general public although awareness in the UK is improving through the work of individual patient activists and groups like the British Lung Foundation (BLF) and the BTS.

Biomarkers/Pathogenesis

A useful biomarker should help to define disease phenotypes, and monitor progression and response to therapy in a reasonable longitudinal time frame. It must also be reproducible and reliable in differentiating patients from healthy subjects. Biomarkers for COPD have been explored in exhaled breath condensate (EBC), induced sputum (IS), broncho-alveolar lavage (BAL), blood and urine. The main pathogenic mechanisms explored include inflammation, oxidative stress and proteolytic balance.

Biomarkers of Inflammation and Oxidative Stress

Neutrophils are characteristically the predominant cell type in induced sputum from COPD patients. Levels of circulating neutrophils are inversely related to FEV₁⁹ and increased induced sputum neutrophil counts have been associated with a more rapid decline in FEV₁.¹⁰ Theophylline significantly reduces induced sputum neutrophils.¹¹ Recent studies suggest that patients with raised induced sputum eosinophils may represent a separate COPD phenotype. COPD patients with raised eosinophil counts in induced sputum and peripheral blood have a better corticosteroid response, which has also been demonstrated in asthma.¹² Peripheral eosinophilia is a risk factor for the development of airways obstruction in those with chronic bronchitis and is an adverse prognostic sign.^{13,14} 8-isoprostane is the product of catalysed lipid peroxidation of arachadonic acid and phospholipids in cell membranes. Induced sputum levels of 8-isoprostane in a cohort of 58 patients showed higher levels in COPD patients of GOLD stage I-III (median 202.2 pg·mL⁻¹) and in healthy smokers (median 108.4 pg·mL⁻¹) compared to non- and ex-smoking controls (median 15.3 pg·mL⁻¹), but it was unable to differentiate between mild COPD and healthy smokers (median 66.6 pg·mL⁻¹). Induced sputum 8-isoprostane correlates significantly with lung function, pack year smoking history and sputum neutrophils.¹⁵

C-reactive protein (CRP) is an acute phase reactant and is raised in several chronic inflammatory conditions.^{16,17} In chronic inflammatory states like diabetes, obesity and IHD, surface adhesion molecules such as ICAM-1 and VCAM-1 are up-regulated on the endothelium, causing leukocyte adhesion and subsequently enhanced chemotaxis. CRP enhances this process and amplifies the inflammatory cascade.¹⁸ CRP and fibrinogen levels are raised in COPD and increase with COPD severity. Mannino et al found a mean CRP level of 4.7mg/l in severe COPD compared to 2.7mg/l in controls.¹⁹ The

Boston early-onset COPD study investigated the heritability of CRP in COPD using linkage analysis. Genetics influenced CRP inheritance in 25% of cases.²⁰

Proteolytic Balance

Neutrophil elastase and matrix metalloproteases (MMPs) induce lung damage through degradation of the extracellular matrix. The integrity of lung tissue is maintained by the pulmonary anti-proteases such as α 1 antiprotease (a1 antitrypsin), secretory leukocyte antiprotease (SLPI) and elafin. MMPs are a zinc dependent family of proteolytic enzymes which have a key role in remodelling of the extracellular matrix. Due to their destructive capacity their gene transcription is tightly regulated. They are released as pro-enzymes and opposed by specific tissue inhibitors of MMPs (TIMPs). When present in excess they result in tissue destruction and are involved in the pathogenesis of destructive lung diseases like COPD, tuberculosis and sarcoidosis.²¹

Studies in COPD patients have measured MMPs in broncho-alveolar lavage (BAL) and lung tissue. Alveolar macrophages in BAL from COPD patients express more MMP-1 and -9 than controls.²² Inflammation increases expression of MMP-9.²³ MMP-7 is an elastase secreted by alveolar macrophages but has not been much studied in COPD.²⁴ The role of MMP-12 in COPD pathogenesis is uncertain. One study found increased levels in current smokers with COPD compared to healthy smokers²⁵ but levels were not increased in COPD patients in two further studies.^{22,26} Immunohistochemistry studies have shown increased MMP-1 expression in COPD, with type I pneumocytes as the key source. A recent review concluded that there is most compelling evidence for the role of MMP-1 and -9 in emphysema, and that, although MMP-9 is more readily detectable, the role of MMP-1 may be more important.²¹ Increased induced sputum MMP-9 was recently associated with an emphysema predominant phenotype on quantitative CT from COPD patients.¹²

Desmosine is a cross-linked amino acid derived from elastin and is a specific marker for elastin degradation. It is filtered completely by the kidney and excreted in the urine. A study of urinary desmosine measured by high performance liquid chromatography (HPLC) showed a greater variability in levels in the COPD group compared to controls but levels did not correlate with spirometry or clinical data.²⁷ A study of 20 COPD patients showed increased desmosine in the COPD group compared to controls with higher levels in those with mild emphysema

on CT compared to more severe emphysema.²⁸ Urinary desmosine levels are higher in alpha-1 antitrypsin deficiency emphysema compared to usual COPD and healthy controls.²⁹ Boschetto et al found higher urinary and induced sputum desmosine levels in COPD patients compared to controls, but found no difference between COPD patients with and without emphysema on thoracic CT.¹²

Prognostic Indicators

Exacerbation Frequency

An acute exacerbation of COPD (AECOPD) is defined clinically as a “sustained worsening of symptoms (breathlessness, sputum volume and sputum purulence)³⁰ which is acute in onset and necessitating a change in medication” in patients known to have COPD.³¹ Hospital admissions for AECOPD are prognostically relevant as there is significant mortality in-hospital and in the year following discharge (in-hospital deaths reported at 8 and 11% and 1 year mortality of 43% and 23% in two studies).^{32,33} AECOPD are associated with poor health status, exercise capacity and increased dyspnoea, with an accelerated decline in FEV₁. 22.9% of patients died within a year of admission with an exacerbation of COPD in a Finnish study of 8325 patients followed up for 10 years.³⁴ In a 3 year study, 23% of patients had no exacerbations requiring steroids or antibiotics suggesting that these patients may represent a particular clinical phenotype.³⁵

Infections (bacterial, viral) account for 50-70% of COPD exacerbations.³⁶ Patients with bacterial colonisation have more exacerbations and may have faster decline in FEV₁. Environmental pollution especially from particulate pollution is thought to be responsible for 9% of admissions for AECOPD.³⁷ Even when symptomatically stable, COPD patients with frequent exacerbations have increased airway inflammation as measured by increased levels of IL-6 and IL-8 in induced sputum.³⁸ After adjusting for confounding factors, secretory leukocyte proteinase inhibitor (SLPI), an endogenous antiprotease with antibacterial and antiviral properties, was found in low levels in patients with frequent exacerbations.³⁹

Physiology

Overinflation of the lungs both static and dynamic is thought to be an important mechanism for the breathlessness associated with COPD and hence exercise tolerance. Inspiratory capacity (IC) is a marker of hyperinflation which has been shown to relate to survival. However, it is difficult to perform and standardise for use

in routine practice.^{40,41} IC/TLC ratio has been shown to grade the severity of COPD and predict outcome.⁴² Cardiopulmonary exercise testing of COPD patients found that peak exercise capacity (V'O_{2,max}) was an independent predictor of mortality.⁴³ Disease of the small airways is pertinent to COPD and can be assessed using the single-breath nitrogen wash-out test (a measure of ventilatory homogeneity) and measurement of airways resistance by forced oscillometry.

Gender

Three year follow-up of the EUROSCOP study reported differences in the clinical course of COPD in men and women, with a greater response to treatment with ICS in men.⁴⁵ In primary care, a study of 1034 patients found that men had higher pack year histories (41 versus 29 pack years) than women and were more likely to have an FEV₁/FVC ratio <70% but that women reported more dyspnoea and were more likely to be taking respiratory medications.⁴⁶ Female smokers particularly with increasing age have an accelerated decline in FEV₁ compared to male current smokers.⁴⁷ A 7 year prospective cohort study of 438 patients on long term oxygen therapy (LTOT) found that women had a 54% higher mortality than men.⁴⁸ Women with COPD have also been found to have higher CRP levels than men.²⁰

BODE Index and Quality of Life Scores

FEV₁ has been the gold standard for assessing COPD severity but it is known that it is not the best indicator of patients' functional abilities. A composite index for staging COPD has been devised using features known to influence outcome in order to gain a more complete assessment of patients and their prognosis. The BODE index is a composite 10-point scoring system based on the clinical indices of Body Mass Index (BMI), airways Obstruction, Dyspnoea and Exercise capacity. A one point increase in the BODE index has been associated with a 34% increase in mortality in COPD and it is a more effective predictor of mortality than FEV₁ alone.⁴⁹ Quality of life measures like the St Georges Respiratory Questionnaire (SGRQ) are also linked to outcome in COPD and may provide useful prognostic information. 3 year follow up of 312 men with COPD found that the SGRQ was an independent predictor of mortality, adjusting for age, FEV₁ and BMI.⁵⁰

Comorbidities

Comorbidity is common in COPD and has been established as an independent predictor of mortality.⁵¹ The SUPPORT study found that 39% of COPD patients had

3 or more comorbidities. A study of 200 COPD patients and 200 matched controls found that COPD patients had an average of 3.7 other chronic comorbidities compared to 1.8 in controls.⁵² A Nordic study found that in patients admitted with AECOPD, 45% had cardiovascular disease, 11% had diabetes and over half of the patients had anxiety and depression as assessed by the Hospital Anxiety and Depression questionnaire (HAD). This has implications for trial design and treatment objectives for COPD.⁵³

Venous thromboembolism (VTE) is associated with a 2-fold increase in death in COPD patients.⁵⁴ VTE was present in 16% of a cohort of 120 COPD patients admitted to hospital with an exacerbation of COPD. A history of recent travel and more severe airways obstruction were associated with VTE.⁵⁵ COPD is associated with increased mortality in community acquired pneumonia (CAP).⁵⁶ Osteoporosis is common in COPD. 68% of a cohort of 62 COPD patients had osteoporosis or osteopenia by bone densitometry and the results could not be explained by corticosteroid use alone.⁵⁷

Cardiovascular Disease

Reduced FEV₁ is an independent predictor of all cause mortality and is associated with increased cardiovascular morbidity and mortality. COPD patients have increased levels of highly sensitive CRP which is associated with higher cardiovascular morbidity. A Canadian study found that cardiovascular events were the main cause of hospital admissions and mortality among COPD patients.⁵⁸ Although respiratory failure is the major cause of death in severe COPD, cardiovascular disease and lung cancer are the leading causes of death in mild/moderate COPD.⁵⁹ In a 15 year follow up of over 16,000 people, the Renfrew and Paisley prospective population study found that poor lung function accounted for 25% of the mortality risk from Ischaemic Heart Disease (IHD).⁶⁰ In a study of 1016 severe COPD patients, cardiac failure significantly contributed to an increase in breathlessness in 26%.⁵²

Treatment

Smoking cessation and long term oxygen therapy for those with respiratory failure have been the only interventions known to reduce mortality from COPD in the last 20 years. Non-pharmacological interventions like pulmonary rehabilitation (PR) now have an established role in the management of moderate and severe COPD. Pulmonary rehabilitation is now known to improve exercise performance and health status in COPD. PR programmes in the UK are generally over-subscribed. Several large randomised controlled trials in pharmacological therapies

for COPD show encouraging results in terms of reducing morbidity and possibly also mortality in COPD.

Combination Inhalers and Anti-Oxidants

Trials of inhaled corticosteroid (ICS), including EUROSCOP, the Copenhagen City Lung Study, the Lung Health Study,⁶² TRISTAN⁶³ and ISOLDE⁶⁴ yielded negative results in terms of effect on decline in FEV₁. It has subsequently become apparent that this is due in part to differences in inclusion criteria, in COPD severity and in end-points used. Macie et al analysed data for 4987 patients following admission for AECOPD. Those treated with ICS within 30 days of hospital discharge had a 25% reduction in all cause mortality, particularly cardiovascular mortality which was reduced by 38%. There is some evidence to suggest that patients treated with bronchodilators but not ICS had higher mortality.⁶⁵ Combined ICS and long acting beta agonist therapy reduces exacerbation rates by 25-30%.⁶⁶ Emerging evidence from the TOWARDS a Revolution in COPD Health (TORCH) study showed a 17% relative reduction in mortality and reduced exacerbation frequency with a combination of ICS and long acting beta agonist, although there was an increase in the incidence of pneumonia in the ICS groups.⁶⁷

Two 1 year trials of treatment with the long acting anticholinergic tiotropium showed a 20-25% reduction in exacerbations.^{68,69} The Understanding the Potential Long-term impacts on Function with Tiotropium (UPLIFT) study,⁷⁰ (results expected in 2008) will also add to knowledge on comorbidities and mortality in COPD. Oral M₃-selective anticholinergics so far show no benefit over inhaled ipratropium.⁷¹ In the PERCEIVE study (1100 patients included, 83,592 households screened), cough was the symptom with the greatest impact on well-being⁷² and yet therapeutic options for the treatment of cough remain limited. Trials of antioxidant and mucolytic therapy with lung function, exercise performance and symptoms as end points have shown little evidence of treatment benefit.⁷³ A randomised placebo controlled trial over 3 years with 523 patients showed no difference in exacerbations frequency.⁷⁴ Mucolytic therapy may however improve symptoms in those with frequent or prolonged exacerbations.

Phosphodiesterase Inhibitors

Theophylline is a bronchodilator and acts by relaxing airway smooth muscle (non-specific inhibitor of phosphodiesterases which break down cyclic-AMP). Higher plasma concentrations (10-20mg/l) are required

for bronchodilation, and these doses often produce side effects limiting tolerability to patients. However, there is increasing evidence of an anti-inflammatory role for theophylline at plasma concentrations of <10mg/l. Corticosteroids recruit histone deacetylase (HDAC) -2 which switches off transcription of inflammatory genes.⁷⁵ HDAC-2 expression and activity is reduced in COPD which may explain why COPD is less ICS responsive than asthma.⁷⁶ Theophylline activates HDACs and therefore may reverse steroid resistance in COPD.^{77,78} A trial is underway to investigate the utility of low dose theophylline in restoring steroid responsiveness in COPD at low plasma concentrations (5mg/l).⁷⁵ Roflumilast and cilomilast are specific phosphodiesterase (PDE)-4 inhibitors. Evidence suggests they may improve FEV₁ compared to placebo.⁷⁹

Retinoids

Emphysema is characterised by destruction of alveolar walls and airspace enlargement resulting in impaired gas exchange and loss of elastic recoil. So far this process has been irreversible. Retinoids are known to be involved in normal lung development and alveolar segmentation in rats models of emphysema.^{80,81} Nuclear hormone receptors like the retinoic acid receptors (subtypes α , β and γ) express genes involved in tissue structure and function. Studies in chronic smoking induced emphysema and elastase induced emphysema in rats have shown response to selective retinoid treatment where there has been alveolar repair and improvement in gas exchange.⁸² Small trials of all-trans retinoic acid (ATRA) in COPD have shown a reduction in elastin fragments, proteases and inflammatory cells in BAL and reduction of desmosine, tropo-elastin, MMP-9, MMP-12, MMP-9/TIMP ratio in lung tissue.⁸³ This suggests that retinoids may reverse the proteolytic imbalance in emphysema.⁸⁴ Larger trials in COPD are awaited.

Future directions

The use of spirometric criteria for COPD diagnosis has been an important step forward. International consensus on the definition of COPD in name and spirometric criteria would help consolidate COPD management strategies, particularly at the primary care level. Continued education of health care professionals is required to improve the quality of epidemiological data available in order to promote COPD to its rightful place on the political agenda. In the UK COPD now features on the GP contract. Detection of undiagnosed COPD is imperative in order to appropriately direct smoking

cessation effort and therapeutic intervention. Biomarkers do not yet provide clear surrogate markers of disease severity and progression. A biomarker which for example predicts smokers at risk of developing COPD is yet to be discovered. There is scope for improving treatment strategies in COPD. Combination inhalers are now known to impact on exacerbation frequency, prevent decline in FEV₁ and possibly even reduce mortality. Delineation of appropriate management of mild/moderate COPD particularly with regard to the use of currently available therapies should be an early focus of research. More aggressive management of comorbidities in COPD, particularly cardiovascular disease, may impact on mortality.

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EDUCATIONAL ARTICLE QUESTIONS

What is New in COPD?

Select the most appropriate true or false answers from the following:

1. The following have been associated with prognosis in COPD:

- a) Inspiratory capacity to total lung capacity ratio
- b) The BODE index
- c) Serum C-reactive protein levels
- d) Forced vital capacity
- e) Comorbidities

2. The following are features of COPD:

- a) FEV1 <80% predicted post bronchodilator
- b) Symptoms of cough and sputum production in smokers
- c) Full reversibility to bronchodilators
- d) A fixed obstructive ventilatory defect
- e) Frequent exacerbations associated with decline in FEV1

3. The following are true about treatments for COPD:

- a) Long acting anticholinergic treatment reduces exacerbation frequency
- b) Long term oxygen therapy and smoking cessation are the only treatments known to reduce mortality in COPD
- c) Mucolytic therapy may improve symptoms in COPD patients with frequent exacerbations
- d) Pulmonary rehabilitation improves health status and exercise performance and should be considered in treatment of moderate COPD
- e) Theophylline is a specific phosphodiesterase-4 inhibitor with bronchodilator and anti-inflammatory properties

4. The following statements concerning biomarkers in COPD are true:

- a) The predominant cell type in induced sputum in COPD is the eosinophil
- b) C-reactive protein is an acute phase reactant which amplifies the inflammatory cascade and is increased in COPD
- c) 8-isoprostane is a marker of oxidative stress which is found in increased levels in induced sputum from COPD patients
- d) Matrix metallo-proteinases prevent tissue destruction in COPD
- e) Alpha-1 antitrypsin protects the lungs from neutrophil elastase

5. Acute exacerbations of COPD are associated with:

- a) Increased mortality
- b) Poor health status and exercise capacity
- c) An infective agent (bacteria or virus) in 20% of cases
- d) Air pollution
- e) Cardiovascular disease

To view the correct answers to the questions, go to Page 57.

RCPSG DIARY OF EVENTS

May 2007 - December 2007

| | |
|---------------------|---|
| 11.05.07 | 24th TC White Symposium "Be All You Can Be!" - Expanding Roles for the Dental Team |
| 25.05.07 | Inverness Symposium |
| 11.06.07 | So You Want To Be A Doctor? |
| 21.06.07 | So Now You Are A Doctor! |
| W/c 27.08.07 | Basic Surgical Skills Course 1 - Malta |
| W/c 27.08.07 | Basic Surgical Skills Course 2 - Malta |
| 05.09.07 - 07.09.07 | Basic Surgical Skills Course A |
| 12.09.07 - 14.09.07 | Basic Surgical Skills Course B |
| 14.09.07 | Pelvic Floor Problems |
| 19.09.07 - 21.09.07 | Basic Surgical Skills Course |
| 26.09.07 & 27.09.07 | Intercollegiate MRCS Examiners Course |
| 09.10.07 | Travel Medicine |
| 10.10.07 | Glasgow Autumn Lung Conference & The Burns Lecture |
| 12.10.07 | Military Surgery Study Day |
| 19.10.07 | Dental Primary Care Practitioners Symposium - Treatment Planning Issues in Primary Dental Care |
| 23.10.07 & 24.10.07 | IMPACT Course |
| 25.10.07 | Medicine for Older People Symposium |
| 25.10.07 | Arthroscopy Skills Course |
| 29.10.07 | Dental Examiners Training Day 07-08 |
| 31.10.07 | Surgical Anastomosis Techniques 07-08-1 |
| 01.11.07 & 02.11.07 | Glasgow Surgical Forum |
| 07.11.07 - 09.11.07 | Basic Surgical Skills Course 07-08-1 |
| 09.11.07 | Medical Update - Renal Medicine & Palliative Care |
| 12.11.07 | Update Course for Optometrists |
| 21.11.07 | RCPSG Dumfries Symposium |
| 23.11.07 | Dental Fellows & Members Symposium following ABM - Microbiology for the Clinical Dental Specialties |
| 10.12.07 & 11.12.07 | IMPACT Course |
| 13.12.07 | Glasgow Medical Forum |

ANSWERS TO EDUCATIONAL ARTICLE QUESTIONS**What is New in COPD?**

The correct answers are as follows:

| Question 1 | Question 2 | Question 3 | Question 4 | Question 5 |
|------------|------------|------------|------------|------------|
| a) T | a) T | a) T | a) F | a) T |
| b) T | b) T | b) F | b) T | b) T |
| c) F | c) F | c) T | c) T | c) F |
| d) F | d) T | d) T | d) F | d) T |
| e) T | e) T | e) F | e) T | e) F |