

COPD Research Review

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Issue 49 - 2019

In this issue:

- > Midlife cardiorespiratory fitness and the long-term risk of COPD
- > A novel biophysical tool to probe disease severity in COPD
- > Circulating neutrophil levels predict pneumonia risk
- > Trends over time in COPD treatments in France
- > Spirometric indices of early airflow impairment in individuals at risk for COPD
- > COPD overdiagnosis in primary care
- > Do COPD treatment choices correspond to specific clinical characteristics?
- > Exacerbations and blood eosinophils in two COPD populations

Abbreviations used in this issue:

COPD = chronic obstructive pulmonary disease;
FEV₁ = forced expiratory volume in 1s; **FVC** = forced vital capacity;
GOLD = Global Initiative for Chronic Obstructive Lung Disease;
ICS = inhaled corticosteroid; **LABA** = long-acting beta agonist;
LAMA = long-acting muscarinic antagonist;
SAMA = short-acting muscarinic antagonist.

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Welcome to the latest issue of COPD Research Review.

In this issue, a Danish study reports that good cardiorespiratory fitness in middle age reduces the long-term risk of COPD, a US study suggests that sputum microstructure may be a novel indicator of COPD progression and severity, and a meta-analysis reports that blood neutrophils may be a useful marker for defining treatment pathways in COPD. An analysis of the COLIBRI-COPD French cohort suggests that new COPD treatment guidelines and recommendations have had a rapid impact on clinical practice in France, and a retrospective study in the UK reports the prevalence of COPD overdiagnosis in primary care.

We hope you find these and the other selected studies interesting and welcome any feedback you may have.

Kind Regards,

Dr Philip Lee

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Midlife cardiorespiratory fitness and the long-term risk of chronic obstructive pulmonary disease

Authors: Hansen G et al.

Summary: This Danish study examined the association between good midlife cardiorespiratory fitness (CRF) and the future risk of COPD. 4730 middle-aged men were recruited in 1970–1971 and followed for up to 46 years. Categories of low, normal or high midlife CRF were defined according to maximal oxygen uptake on an ergometer test. Compared with participants with low midlife CRF, the estimated risk of incident COPD was 21% lower with normal CRF and 31% lower with high CRF. The risk of death from COPD was 35% lower with normal midlife CRF and 62% lower with high CRF than with low CRF. Analysis of survival data showed a delay to incident COPD and death from COPD in the magnitude of 1.3–1.8 years in participants with normal and high CRF compared with those with low CRF.

Comment: Previous studies have shown associations between higher physical activity and higher indices of lung function, as well as lower incidence of COPD. This Danish study showed a lower risk of COPD and consequential mortality in patients with higher CRF, determined as maximal oxygen uptake on an ergometer test. Developing a plan for regular physical exercise and enrollment in pulmonary rehabilitation programmes will improve the functional and psychological status of symptomatic COPD patients.

Reference: *Thorax* 2019;74(9):843-48

[Abstract](#)

Nanoparticle diffusion in spontaneously expectorated sputum as a biophysical tool to probe disease severity in COPD

Authors: Chisholm J et al.

Summary: This study evaluated the hypothesis that a tightened mesh structure within spontaneously expectorated sputum contributes to increased COPD disease severity. The mesh size of sputum was quantified by muco-inert nanoparticle diffusion for 33 samples collected from COPD and non-COPD individuals. The mobility of muco-inert nanoparticles was more hindered in sputum samples from patients with severe COPD, suggesting a tighter mucus mesh size.

Comment: Airway mucus comprises a complex mixture of high molecular weight mucin glycoproteins, cells, cellular debris, bacterial proteins and antibacterial products. Alterations in the composition of mucus may result in dysfunctional mucociliary clearance and development of airway diseases. This American study showed mobility of muco-inert nanoparticle diffusion was hindered in severe COPD. Nanoparticle mobility has been shown to correlate with measurements of lung function. These findings suggest sputum microstructure, as quantified by muco-inert nanoparticle diffusion, may serve as a novel indicator for COPD severity and progression.

Reference: *Eur Respir J* 2019;54(2):1900088

[Abstract](#)

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Circulating neutrophils levels are a predictor of pneumonia risk in chronic obstructive pulmonary disease

Authors: Pascoe S et al.

Summary: This meta-analysis investigated the use of circulating neutrophil levels as a predictor of pneumonia risk in patients with COPD. A search of the GlaxoSmithKline trial registry identified 10 randomised, double-blind studies (n=11,131) that compared an ICS arm with a control arm, measured baseline blood neutrophil levels, and had a duration of ≥ 24 weeks. ICS and non-ICS cohorts were well matched in terms of neutrophil distribution and demographics. Meta-analysis of the data showed that increasing neutrophil count was associated with an increased proportion of patients with pneumonia. Patients below the median neutrophil count had a 25% lower risk of a pneumonia event, and had a longer time to a first event, than patients at or above the median.

Comment: Use of ICS in COPD is linked with an increased risk of pneumonia. Neutrophils are effector cells in the pathogenesis of COPD as inflammation in COPD is characterised by neutrophils, macrophages and CD8+ T cells. This post hoc analysis focused on 10 COPD clinical trials and found that increased blood neutrophils in COPD could potentially be utilised as a biomarker for patients with a high risk of pneumonia, especially when ICS therapy was required. However, the exact nature of the association between neutrophils and pneumonia risk was not well defined in this analysis and increased neutrophil counts could occur secondary to infection or be directly driven by the underlying COPD inflammatory process.

Reference: *Respir Res* 2019;20:195
[Abstract](#)

Trends over time in COPD treatment choices by respiratory physicians

Authors: Roche N et al.

Summary: This analysis of the French COLIBRI-COPD cohort evaluated trends over time in COPD treatment choices by respiratory physicians. Inhaled drug treatments were classified into 5 treatment categories: no initial maintenance treatment (untreated, or only SAMA or SABA); one long-acting bronchodilator (LABA or LAMA); two long-acting bronchodilators (LABA + LAMA); one long-acting bronchodilator + ICS (LABA or LAMA + ICS); two long-acting bronchodilators + ICS (LABA + LAMA + ICS). Data were collected from 4537 patients from February 2012 to November 2018. Three major changes were observed over time: an increase in treatment category "no initial maintenance treatment", mostly for GOLD 1 or GOLD A categories; an increase in treatment category "two long-acting bronchodilators" for GOLD 2–4 and GOLD A–D categories; and a decrease in ICS use, mostly for GOLD 1–3 and GOLD A categories.

Comment: COPD management is evolving with numerous significant guideline updates over the last decade. This French study highlighted a significant decline in ICS use with increasing use of dual bronchodilator (LAMA/LABA) therapy. Compared with the available COPD treatments a decade ago, there is a greater variety of treatment options available in Australia to maximise bronchodilation. With the demonstrated efficacy and good safety profile of fixed-dose combination LAMA/LABA in COPD, most guidelines are now recommending the use of dual bronchodilation prior to introducing ICS with the aim of minimising ICS-related side effects.

Reference: *Respir Med* 2019;156:8-14
[Abstract](#)

Spirometric indices of early airflow impairment in individuals at risk of developing COPD: spirometry beyond FEV₁/FVC

Authors: Hoesterey D et al.

Summary: Clinically relevant airway abnormalities may precede the formal diagnosis of COPD by FEV₁/FVC ratio. This review discussed the theoretical ability of spirometry to capture fine pathophysiological changes in individuals at risk of developing COPD, and reviewed existing evidence for spirometric measures that may be used to better detect early airflow impairment.

Comment: COPD is traditionally defined as airflow limitation that is not fully or substantially reversible after bronchodilation. However, the full potential of spirometry to identify early COPD is not well explored. Spirometry can potentially identify subtle pathophysiological changes in early COPD and better capture early airflow impediment. This review article highlighted potential spirometric measurements to identify early airflow impediment (FEV₁/FEV₆ or FEV₃/FEV₆). Sophisticated curve analysis could potentially detect subtle patterns to differentiate between early pathophysiological changes and physiological decline with ageing.

Reference: *Respir Med* 2019;156:58-68
[Abstract](#)

COPD overdiagnosis in primary care

Authors: Josephs L et al.

Summary: This retrospective study analysed the UK Care and Health Information Analytics database to evaluate the prevalence of COPD overdiagnosis in primary care. Medical records for 14,378 patients with a diagnosis of COPD and a median COPD duration of 60 months were reviewed. FEV₁/FVC had been recorded in 86.9% of patients (median 5 measurements). Serial ratios of FEV₁/FVC from time of initial COPD diagnosis were used to assign patients to one of three airflow obstruction categories, according to whether all (persistent), some (variable) or none (absent) were $< 70\%$ predicted. 52.4% of patients were found to have persistent airflow obstruction, 36.1% had variable airflow obstruction and 11.5% had absent airflow obstruction. Being female, never smoking, having higher body mass index or more comorbidities were significant predictors of absent and variable airflow obstruction. 57% of patients with absent airflow obstruction received long-acting bronchodilators and 60% received an ICS.

Comment: Spirometry is the gold standard for measurement of airflow obstruction which aids establishment of COPD diagnosis. However, there are ongoing concerns that a definitive COPD diagnosis has not been achieved in a significant proportion of patients prior to dispensing respiratory medications. This UK retrospective analysis showed about 25% of patients receiving respiratory medications had no consistent evidence of airflow obstruction. COPD is often misdiagnosed and other comorbidities such as cardiovascular diseases, metabolic syndrome and lung cancer could be confused with COPD. Diagnosis based on symptoms and history alone is likely to miss up to 50% of COPD cases. Therefore, spirometry is necessary for objective assessment of airflow limitation and allows early detection of COPD.

Reference: *NPJ Prim Care Respir Med* 2019;29:33
[Abstract](#)

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LABA: long-acting β₂-agonist. LAMA: long-acting muscarinic antagonist. COPD: chronic obstructive pulmonary disease.

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Are there specific clinical characteristics associated with physician's treatment choices in COPD?

Authors: Roche N et al.

Summary: This study determined whether COPD treatment choices made by respiratory physicians correspond to patients' specific clinical characteristics. 1171 patients who had complete treatment and clinical characterisation data were included. Multiple statistical models were applied to explain 5 treatment categories: A: no COPD treatment or short-acting bronchodilator(s) only; B: one long-acting bronchodilator (LABA or LAMA); C: LABA+LAMA; D: a LABA or LAMA + ICS; E: triple therapy (LABA+LAMA+ICS). Mean FEV₁ was 60% predicted. 32.9% of patients were prescribed triple therapy, 29.8% received a combination of two treatments (treatment categories C or D), and 44% of patients received an ICS-containing regimen. Single or dual bronchodilation (treatment categories B and C) were used in 19% of patients each.

Comment: ICS were overused in a high proportion of early COPD patients which is not supported by guidelines or indication for ICS in COPD. Approximately 70% of COPD patients treated with maintenance therapy are prescribed a LABA/ICS in Australia. This French study aimed to determine if COPD pharmacological choices by respiratory physicians correspond to appropriate patients' features. It showed triple therapy (ICS/LABA/LAMA) was prescribed for 33% of patients whilst ICS-containing therapy was prescribed for 44% of patients. Of concern, single or dual bronchodilation were less frequently prescribed. Triple therapy with ICS is restricted to certain COPD subgroups most likely to benefit (FEV₁ <50% predicted prior to therapy and a history of repeated exacerbations with significant symptoms despite regular bronchodilator therapy with LAMA + LABA or ICS + LABA) and treatment must be for symptomatic management. As of August 2018, there have been changes to the PBS restrictions of COPD medicines. The change in restriction was made as there was a high proportion of COPD patients initiated on ICS/LABA therapies, which is not recommended in national or international guidelines.

Reference: *Respir Res* 2019;20:189

[Abstract](#)

Evaluation of exacerbations and blood eosinophils in UK and US COPD populations


Authors: Vogelmeier C et al.

Summary: This retrospective cohort analysis evaluated blood eosinophil counts and exacerbations in two COPD cohorts. Data for 15,364 COPD patients on the UK Clinical Practice Research Datalink (CPRD) database and 139,465 on the US Optum database were reviewed. Among 3089 patients from CPRD and 13,414 from Optum who had ≥2 exacerbations and available eosinophil counts in the baseline period, 17.0% and 13.3%, respectively, had an eosinophil count ≥400 cells/μL. 82.8% of CPRD patients and 80.6% of Optum patients with ≥2 exacerbations or an eosinophil count ≥400 cells/μL during the first year exacerbated at least once in the follow-up year, and 76.8% and 76.5%, respectively, continued to have an eosinophil count ≥300 cells/μL in the follow-up year. Approximately 10% of patients had both ≥2 exacerbations and an eosinophil count ≥300 cells/μL across the two databases.

Comment: Previous studies have suggested that the risk of COPD exacerbations increased with blood eosinophil counts, and blood eosinophil counts may serve as a biomarker for exacerbation risk. This retrospective cohort analysis showed significant variability in blood eosinophil counts over two consecutive years with only 10% of COPD patients having frequent exacerbations and eosinophil count ≥300 cells/μL. Elevated blood eosinophil count should be confirmed by a repeat measurement 4–6 weeks after the initial assessment. Eosinophil count should be measured 4–6 weeks after cessation of oral corticosteroids as oral corticosteroids are known to suppress eosinophil counts.

Reference: *Respir Res* 2019;20:178

[Abstract](#)



Independent commentary by Dr Philip Lee, MBBS (Hons) FRACP.
Dr Philip Lee is a Respiratory and Sleep Physician currently working at the St. George Hospital Centre for Sleep Disorders & Respiratory Failure in Sydney. His research interests include non-invasive ventilation, respiratory failure and sleep disordered breathing.

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