COPD Research Review™

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Issue 47 - 2019

In this issue:

Abbreviations used in this issue:

ARF = acute respiratory failure; **BMI** = body mass index; **CODEX** = Comorbidity, Obstructive Dyspnoea, Exacerbations; **COPD** = chronic obstructive pulmonary disease; **FEV_1** = forced expiratory volume in 1s; **GOLD** = Global Initiative for Chronic Obstructive Lung Disease; **HFNC** = high-flow nasal cannula; **HR** = hazard ratio; **ICS** = inhaled corticosteroid; **LABA** = long-acting beta agonist; **LAMA** = long-acting muscarinic antagonist.

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Welcome to the latest issue of COPD Research Review.

In this issue, real-world evidence shows that combined LABA/LAMA inhalers are as effective as LABA/ICS inhalers in preventing COPD exacerbations, a study in Vietnam supports the vital role of pharmacists alongside physicians in the management of COPD, and an analysis of the COLUMBUS trial determines predictors of response to maintenance azithromycin in COPD patients with frequent exacerbations. A Chinese study reminds us of the harmful effects of ambient fine particulate matter, a Japanese study shows that LAMA/LABA combination therapy improves dynamic lung hyperinflation in COPD, and an observational study in 14 low- to middle-income countries finds that individuals with a lower BMI are more at risk for COPD than those with a higher BMI.

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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Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice

Authors: Suissa S et al.

Summary: This study used data from the UK Clinical Practice Research Datalink to compare the real-world effectiveness and safety of LABA/LAMA vs LABA/ICS combinations in patients aged ≥55 years with COPD. 1977 initiators of LABA/LAMA therapy in 2002–2015 were matched with 1977 initiators of LABA/ICS therapy and were monitored for 1 year for the occurrence of a moderate or severe COPD exacerbation and severe pneumonia. The hazard ratio of moderate or severe COPD exacerbation associated with LABA/LAMA initiation relative to LABA/ICS initiation was 1.04, and for a severe exacerbation was 0.94. The incidence of severe pneumonia requiring hospitalisation was lower with LABA/LAMA therapy (HR, 0.66).

Comment: Previous trials have linked ICS use in COPD to an increased risk of pneumonia, with local and systemic side effects of oral candidiasis, hoarse voice and skin thinning/easy bruising. Other observational studies have also suggested ICS use increases the risk of cataracts, tuberculosis and diabetes. This cohort study utilised data from the UK Clinical Practice Research Datalink with the aim of assessing a real-world comparative effectiveness and safety between LABA/LAMA and LABA/ICS combination therapy. It found the risk of severe pneumonia requiring hospitalisation was lower with LABA/LAMA inhalers than LABA/ICS inhalers whilst both treatments appear effective in preventing COPD exacerbations. The Australian COPD-X guidelines recommend adding ICS only in symptomatic patients despite optimised bronchodilation with LAMA/LABA therapy with FEV_1 <50% predicted and at least 2 exacerbations in the last 12 months.

Reference: Chest 2019;155(6):1158-65

Abstract

Impact of pharmaceutical care in the improvement of medication adherence and quality of life for COPD patients in Vietnam

Authors: Nguyen T-S et al.

Summary: This study in Vietnam evaluated the impact of a pharmacist-led pharmaceutical care programme on medication adherence and quality of life in COPD patients over a 1-year period. 211 COPD patients received brief counselling by pharmacists that focused on the role of COPD medications and the importance of adherence. Patient adherence was evaluated using the Morisky Medication Adherence Scale, quality of life was assessed using the EQ-5D-5L questionnaire, and clinical outcomes were evaluated by symptom scores. The percentage of patients with good adherence increased from 37.4% at baseline to 53.2% at 12 months ($p<0.001$). Mean medication adherence scores improved from 6.7 at baseline to 7.4 at study end ($p<0.001$), and EQ-5D-5L index values improved from 0.47 to 0.59 ($p<0.001$). Symptom scores did not change significantly during the study period.

Comment: Unintentional non-adherence arises due to practical barriers to treatment, such as language barriers, forgetfulness, inadequate understanding of instructions and most importantly, poor inhaler technique. Intentional non-adherence occurs as a result of patient choice in taking less medication than prescribed or taking it differently than prescribed. This can arise due to concerns about side effects, patient beliefs that conflict with or undermine confidence in conventional COPD therapies, social pressure or skipping doses to save on treatment costs. Despite best efforts and interventions by medical practitioners, non-adherence to treatment remains a major issue in COPD. This Vietnamese study showed involvement of pharmacists in a pharmaceutical care programme with appropriate counselling resulted in improvement of medication adherence and quality of life in COPD patients. Pharmacists could act as a vital link between medical practitioners and COPD patients by providing structured education with regular reinforcement of correct inhaler technique.

Reference: Respir Med 2019;153:31-7

Abstract

Blood eosinophil count and GOLD stage predict response to maintenance azithromycin treatment in COPD patients with frequent exacerbations

Authors: Djamin R et al.

Summary: This analysis of the COLUMBUS trial determined predictors of response to maintenance treatment with azithromycin in COPD patients with frequent exacerbations. 92 patients were randomised to receive azithromycin or placebo for 1 year in a double-blind design. In the azithromycin group, a significantly lower number of exacerbations was observed in patients with baseline blood eosinophil count ≥2.0% vs < 2.0%, GOLD stage 1–2 vs GOLD stage 4, and GOLD group C vs GOLD group D. The number of hospitalisations was significantly lower in patients with a blood eosinophil count ≥2.0% vs <2.0%, and in patients with GOLD stages 1–2 vs stage 4 COPD.

Comment: Blood eosinophils serve as a potential therapeutic biomarker of ICS response in COPD with evidence suggesting that patients with blood eosinophils >300 cells/μL are most likely to benefit from ICS. Previous studies showed azithromycin use in COPD reduced the frequency of exacerbations with improvement in quality of life. This post hoc analysis utilised data from the COLUMBUS trial, focused on the characteristics of COPD patients reporting best response to azithromycin maintenance treatment. It found COPD patients with frequent exacerbations in GOLD stage 1–2 or GOLD group C and patients with blood eosinophil count ≥2% benefitted most from azithromycin maintenance in preventing COPD exacerbations and reducing the number of hospitalisations due to COPD exacerbations. Blood eosinophils should be used in combination with clinical judgement, taking into account FEV_1 and exacerbation history. In view of the side effects of azithromycin, including antimicrobial resistance, hearing impairment and cardiac arrhythmias, these vital findings will define the phenotype of COPD patients for azithromycin maintenance therapy.

Reference: Respir Med 2019;154:27-33
Abstract

An accurate prediction model to identify undiagnosed at-risk patients with COPD

Authors: Su K-C et al.

Summary: This cross-sectional Taiwanese study used a COPD prediction model to identify at-risk, undiagnosed COPD patients. 147 patients with COPD and 154 patients without COPD were included in the development cohort. Four independent variables (age, smoking pack-years, CAT score, and percent predicted peak expiratory flow rate [PEFR]) were incorporated into the prediction model to estimate COPD probability (PCOPD). A PCOPD of ≥0.65 identified COPD patients with high specificity (90%), and a large proportion (91.4%) of patients with clinically significant COPD.

Comment: COPD is often undiagnosed or misdiagnosed and accurate diagnosis of COPD is often late. Signs and symptoms may be subtle and are attributed to ageing or other comorbidities, compounded by significant underuse of spirometry. This Taiwanese study focused on development of a COPD prediction model to identify at-risk, undiagnosed COPD patients aged ≥40 years with respiratory symptoms and a smoking history (≥20 pack-years). It found that a prediction model incorporating age, smoking pack-years, CAT score and percent predicted PEFR can identify COPD patients with high specificity and identify the majority of patients with clinically significant COPD. Early COPD diagnosis enables timely implementation of effective interventions, including smoking cessation, exercise and pulmonary rehabilitation, influenza/pneumococcal vaccination and appropriate pharmacotherapy.

Reference: NPJ Prim Care Respir Med 2019;29:22
Abstract

Role of $PM_{2.5}$ in the development and progression of COPD and its mechanisms

Authors: Zhao J et al.

Summary: This Chinese study investigated the role of ambient fine particulate matter <2.5μm in diameter ($PM_{2.5}$) in the development of COPD. Prolonged chronic exposure to $PM_{2.5}$ was found to decrease lung function and cause emphysematous lesions and airway inflammation in a dose-related manner in a Chinese Han population. $PM_{2.5}$ and cigarette smoke had a synergistic effect on COPD development and progression.

Comment: Fine particulate matter ($PM_{2.5}$) is a mix of solid and liquid particles in the air and results in higher susceptibility to asthma, COPD and lung cancer. This Chinese study highlighted the harmful effects of $PM_{2.5}$ exposure, including induction of pulmonary inflammation, aggravation of cigarette smoke-induced changes, reduction in lung function which results in emphysema. Previous studies have shown that increased exposure to $PM_{2.5}$ is associated with increased morbidity and mortality from chronic respiratory diseases including COPD. This may be accounted for by $PM_{2.5}$-activated inflammatory cascades, resulting in epithelial damage and consequential lung injury.

Reference: Respir Res 2019;20:120
Abstract

High flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease with acute-moderate hypercapnic respiratory failure

Authors: Sun J et al.

Summary: This retrospective Chinese study investigated the use of high-flow nasal cannula (HFNC) oxygen therapy in COPD patients with hypercapnic acute respiratory failure (ARF). Outcomes for 82 COPD patients with moderate hypercapnic ARF (arterial blood gas pH 7.25–7.35 and $PaCO_2$ >50mm Hg) who received HFNC (n=39) or non-invasive ventilation (NIV; n=43) in an intensive care unit in 2016–2018 were reviewed. Treatment failure (need for invasive ventilation or a switch to the other study treatment) occurred in 28.2% of patients receiving HFNC oxygen therapy compared with 39.5% of patients receiving NIV. No significant between-group differences were seen for 28-day mortality (15.4% vs 14%, respectively). The number of nursing airway care interventions in the HFNC group was significantly less than that in the NIV group in the first 24h of treatment, while the duration of device application was longer in the HFNC group. Skin breakdown was more common in patients receiving NIV (20.9% vs 5.1%; p<0.05).

Comment: NIV has been the standard of care in COPD patients with acute hypoxic hypercapnic respiratory failure and respiratory acidosis with mortality benefits. HFNC oxygen is applied in acute hypoxic respiratory failure with proven success. This retrospective Chinese study focused on COPD patients with moderate hypercapnic ARF and showed no significant difference of treatment failure in patients receiving HFNC or NIV. Potential benefits of HFNC may include less nursing intervention or skin breakdown. Future studies should aim to define the phenotype of COPD patients with ARF who are most likely to benefit from HFNC.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:1229-37
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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LABA: long-acting β_2-agonist. LAMA: long-acting muscarinic antagonist. COPD: chronic obstructive pulmonary disease.

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References: 1. ULTIBRO® BREEZHALER® 110/50 Approved Product Information. February 2018. **2.** Wedzicha JA *et al. Lancet Respir Med* 2013;1:199–209. **3.** Wedzicha JA *et al. N Engl J Med.* 2016; 374:2222-2234. **4.** Seretide® Approved Product Information. **5.** Spiriva® Approved Product Information. **6.** Spiriva® Respimat® Approved Product Information.

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Efficacy of tiotropium and olodaterol combination therapy on dynamic lung hyperinflation evaluated by hyperventilation in COPD

Authors: Kawachi S & Fujimoto K

Summary: This open-label Japanese study evaluated the efficacy of inhaled tiotropium + olodaterol combination therapy on dynamic lung hyperinflation (DLH) in patients with COPD. 33 patients with mild to moderate COPD received tiotropium/olodaterol 5/5μg via a soft-mist inhaler once daily for 8 weeks. The primary outcome was defined as a decrease in inspiratory capacity from rest evaluated by metronome-paced incremental hyperventilation (MPIH; an index of DLH). Decreasing inspiratory capacity by MPIH was significantly reduced by tiotropium/olodaterol, with a mean change from baseline of about −0.11 to −0.13ml at week 8 ($p<0.05$). COPD Assessment Test (CAT) score, FEV_1, and 6-min walk distance (6MWD) also improved significantly with treatment.

Comment: DLH is a key determinant of symptomatology and exercise intolerance in COPD. This abnormal physiological response occurs in moderate-to-severe COPD patients when end-expiratory lung volume increases under conditions of greater minute ventilation, like physical exercise. Variability of DLH offers an opportunity for treatment intervention to slow or reverse hyperinflation. Long-acting bronchodilators can result in significant improvements in hyperinflation in COPD. This Japanese study showed that LAMA/LABA combination therapy with tiotropium + olodaterol improved DLH in COPD, along with 6MWD and CAT score. Reducing hyperinflation in COPD patients is a vital mechanism for improving exercise tolerance and activity level.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:1167-76
Abstract

External validation and recalculation of the CODEX index in COPD patients

Authors: Almagro P et al.

Summary: This study validated the CODEX index in a large population of COPD patients. 3321 patients who were followed up for a median 1064 days (11,190 person-years) in various studies were included in the validation cohort. The CODEX index was found to be statistically associated with mortality in the short-term (≤3 months), medium-term (≤1 year) and long-term (10 years), with an area under the curve of 0.72, 0.70 and 0.76, respectively. Recalculating the thresholds of the CODEX index using the cut-offs of variables previously suggested in the 3CIA study (mCODEX index) gave better performance than the original CODEX index for medium-term mortality.

Comment: The CODEX index is a prognostic scoring system in COPD. It is composed of the combination of FEV_1%, dyspnoea, and number of severe COPD exacerbations in the previous year, stratified according to the BODE (Body mass index, Obstructive, Dyspnoea, Exercise) and BODEX thresholds (Body mass index, Obstructive, Dyspnoea, Exacerbations). This cohort study analysed pooled data from 26 cohort studies and the COPD Cohorts Collaborative International Assessment (3CIA) consortium database to calculate the CODEX and mCODEX indices for COPD patients. mCODEX replaces CODEX thresholds for FEV_1% and dyspnoea (modified scale of the Medical Research Council) with the previously suggested cut-offs based on survival prediction analysis in 3CIA. It found both the CODEX and mCODEX index can reliably predict mortality in COPD. Such multicomponent scales can allow estimation of mortality in COPD patients and direct appropriate resources to patients with a high predicted mortality risk.

Reference: COPD 2019;16(1):8-17
Abstract

Low body mass index is associated with higher odds of COPD and lower lung function in low- and middle-income countries

Authors: Grigsby M et al.

Summary: This study evaluated the association between BMI, lung function, and COPD in 14 low- and middle-income countries. Data for 12,396 individuals aged 35–95 years were analysed by multivariable regression (adjusted for confounding factors). An inflection point was observed at BMI 19.8 kg/m^2; participants with BMI below this level had a 2.28 greater risk of having COPD and had poorer lung function than those with BMI ≥19.8 kg/m^2. The association between BMI and lung function remained even after excluding participants with COPD.

Comment: Cigarette smoking is the most important risk factor for COPD and socioeconomic status is a strong determinant of health. Low BMI has been considered as a potential risk factor for development of COPD. Previous studies have demonstrated a lower prevalence of COPD in patients with high BMI. This observational study focused on 14 low- to middle-income countries where low BMI (underweight) is more prevalent. It showed individuals with a lower BMI were more likely to have COPD and had lower lung function compared to those with a higher BMI, even after excluding patients with COPD. Being underweight is also associated with higher mortality in COPD, and BMI should be taken into consideration when managing patients with COPD.

Reference: COPD 2019;16(1):58-65
Abstract

Human rhinovirus impairs the innate immune response to bacteria in alveolar macrophages in chronic obstructive pulmonary disease

Authors: Finney L et al.

Summary: This *in vitro* study investigated the effect of human rhinovirus (HRV) on phagocytosis and cytokine response to bacteria by alveolar macrophages and monocyte-derived macrophages (MDM) obtained from COPD patients and healthy controls. Macrophages were exposed to HRV16 or medium control for 24 hours. Phagocytosis of fluorescently labelled *Haemophilus influenzae* or *Streptococcus pneumoniae* was assessed by fluorimetry. Cytokine response (interleukin [IL]-8, IL-6, tumour necrosis factor-α, and IL-10) was measured by ELISA. HRV significantly impaired phagocytosis of *H. influenzae* by 23% in MDM and by 18% in alveolar macrophages from COPD patients. HRV also significantly reduced phagocytosis of *S. pneumoniae* by 33% in MDM from COPD patients, but had no effect on phagocytosis of *H. influenzae* or *S. pneumoniae* in healthy controls. HRV significantly reduced cytokine responses to *H. influenzae* in macrophages from COPD patients.

Comment: Most COPD exacerbations are induced by viral respiratory tract infections. HRV infection is the most common viral cause of acute COPD exacerbations. This UK study showed HRV infection results in impairment of phagocytosis of two significant pathogens in COPD (*H. influenzae* and *S. pneumoniae*), leading to bacterial outgrowth. HRV also reduced proinflammatory cytokine response in COPD. HRV infection could result in dysbiosis of the pulmonary microbiome through the phagocytic defect, promoting acute COPD exacerbations or pneumonia.

Reference: Am J Respir Crit Care Med 2019;199(12):1496-1507
Abstract

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