COPD Research Review™

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Issue 44 - 2019

In this issue:

Abbreviations used in this issue:

COPD = chronic obstructive pulmonary disease;
EXACT = Exacerbations of COPD Tool;
FEV_1 = 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.

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Welcome to the latest issue of COPD Research Review.

In this issue, an analysis of the London COPD Cohort study confirms the association between air pollution and viral-type COPD exacerbations, and an analysis of the NHLBI Pooled Cohorts study reports an association between albuminuria and lung function decline. We also present evidence that daily aspirin use decreases the risk of COPD exacerbations, influenza vaccination reduces influenza-related hospitalisations in COPD patients, and vitamin D supplementation reduces COPD exacerbations in patients with vitamin D deficiency.

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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Increased chronic obstructive pulmonary disease exacerbations of likely viral etiology follow elevated ambient nitrogen oxides

Authors: Pfeffer P et al.

Summary: This analysis of the London COPD Cohort study evaluated the association between air pollution and viral-type exacerbations in patients with COPD. Exposure to ambient particulate matter ≤10µm, oxides of nitrogen (NOx), or ozone was reviewed for 4173 exacerbations occurring over a 20-year period. Regression analysis adjusted for temperature, seasonality, and long-term trend showed that higher ambient NOx was consistently associated with increased viral-type exacerbations at 2–4 days lag (p=0.010); recovery was slower after viral-type exacerbations in patients exposed to higher ambient NOx. These findings were replicated in a subset of 2841 exacerbations treated with oral corticosteroids or antibiotics.

Comment: The role of ambient air pollution in the development of COPD remains uncertain. This UK study utilised data from the London COPD Cohort from 1996 to 2015 and highlighted an association between elevated ambient NOx, including nitrogen dioxide/nitric oxide, and an increased incidence of prolonged COPD exacerbations with symptoms of viral aetiology. Significant impact with air pollution was also noted in analyses of exacerbations associated with healthcare utilisation. From a public health perspective, minimising exposure to air pollution could be beneficial for COPD patients as the negative impact of air pollution on COPD exacerbations are readily observed within 5 days after exposure to elevated ambient NOx, as suggested in this epidemiological study.

Reference: Am J Respir Crit Care Med 2019;199(5):581-91

Abstract

Albuminuria, lung function decline, and risk of incident chronic obstructive pulmonary disease

Authors: Oelsner E et al.

Summary: This analysis of the NHLBI Pooled Cohorts study determined the association between albuminuria and chronic lower respiratory diseases. 10,961 participants with preserved lung function were included in the analysis. Adjusted hazards models showed that each standard deviation (SD) increase in log-transformed albuminuria was associated with a 2.81% greater decline in FEV_1 (p=0.0047), an 11.02% greater decline in FEV_1/FVC (p=0.0011), a 15% higher risk of incident moderate to severe COPD (p=0.0021), and a 26% higher risk of COPD-related hospitalisation/mortality (p<0.0001). Albuminuria was not associated with asthma.

Comment: There is a high prevalence of chronic kidney disease amongst COPD patients. Albuminuria, defined by urine albumin to creatinine ratio, is a biomarker of endothelial damage in renal diseases. This study analysed 6 observational cohort studies and showed the presence of albuminuria in COPD patients was associated with greater rate of lung function decline, incident spirometry-defined COPD and COPD-related health consequences. Such associations were independent of smoking status, underlying renal function and cardiovascular disease. The results of this study would support a potential role for endothelial and microvascular mechanisms in the pathogenesis of COPD.

Reference: Am J Respir Crit Care Med 2019;199(3):321-32

Abstract

Capturing exacerbations of chronic obstructive pulmonary disease with EXACT

Authors: Frent S et al.

Summary: This subanalysis of the FLAME study used the EXACT tool to compare the effects of glycopyrronium/indacaterol versus fluticasone/salmeterol on symptom-defined exacerbations. A subgroup of 457 participants in the FLAME study used the EXACT questionnaire to assess the onset, recovery, and magnitude of symptom-defined exacerbations. A nonsignificant 17% reduction in the annualised rate of symptom-defined exacerbations and a numerically longer time to first symptom-defined exacerbation were observed with glycopyrronium/ indacaterol compared with fluticasone/salmeterol (hazard ratio, 0.76; p=0.075). These results were consistent with those seen in the overall FLAME population.

Comment: When initiating appropriate long-acting inhaled medications in COPD, a recent Cochrane systematic review analysing 11 trials (9839 patients) supports the use of LAMA/LABA fixed-dose combinations over ICS/LABA inhalers. Compared to ICS/LABA combination, LAMA/LABA resulted in a reduction in the exacerbation rate and FEV_1 improvement. Of note, the rate of pneumonia is lower amongst LAMA/LABA users with no change in overall mortality. This study analysed glycopyrronium/indacaterol (LAMA/LABA) vs fluticasone/salmeterol (ICS/LABA) in COPD and found that LAMA/LABA prolonged the time to first exacerbation when compared to ICS/LABA. Patients on LAMA or LABA monotherapy with persistent exacerbations may benefit from a step up to a LAMA/LABA or ICS/LABA under the current GOLD guidelines. However, LAMA/LABA is the primary choice as ICS may increase the risk of developing pneumonia.

Reference: Am J Respir Crit Care Med 2019;199(1):43-51
Abstract

Aspirin use and respiratory morbidity in COPD

Authors: Fawzy A et al.

Summary: This analysis of data from the SPIROMICS study investigated the effect of daily aspirin use on COPD exacerbations. Information on daily aspirin use was obtained at baseline from 1698 SPIROMICS participants with COPD. These patients were then followed up for 3 years for acute exacerbations of COPD (AECOPD) that were categorised as moderate (treated with antibiotics or oral corticosteroids) or severe (requiring emergency department visit or hospitalisation). 45% of participants reported daily aspirin use at baseline. Propensity score matching (503 pairs) showed that aspirin users had a lower incidence of total AECOPD (adjusted incidence rate ratio, 0.78). Aspirin use was associated with lower total St. George's Respiratory Questionnaire score, reduced odds of moderate to severe dyspnoea, and lower COPD Assessment Test score. Daily aspirin use had no effect on 6-min walk distance.

Comment: Previous studies have demonstrated that aspirin use is linked with reduced mortality risk in COPD patients. Aspirin reduces pulmonary pro-inflammatory cytokines, as well as attenuating the elevation of inflammatory markers (C-reactive protein and interleukin-6), which are part of the inflammatory phenotype of COPD. This observational cohort study showed self-reported aspirin users had an overall 22% lower incidence of acute COPD exacerbations compared with non-aspirin users after a median follow-up of 2.7 years. Aspirin users also reported better quality of life and less dyspnoea burden. Although there was a 25% reduction in moderate COPD exacerbations, there was no significant difference in severe exacerbations. Of note, stronger association between aspirin use and reduced incidence of COPD exacerbations is noted amongst patients with chronic bronchitis. Future studies of aspirin in COPD should focus on patients with chronic bronchitis.

Reference: Chest 2019;155(3):519-27
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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Effectiveness of influenza vaccination on hospitalizations and risk factors for severe outcomes in hospitalized patients with COPD

Authors: Mulpuru S et al.

Summary: This Canadian study evaluated the impact of influenza vaccination on influenza-related hospitalisations in patients with COPD. Data were analysed from a prospective cohort study of 4198 patients with COPD and known vaccination status who were hospitalised with an acute respiratory illness or exacerbation in 2011–2015. All patients underwent nasopharyngeal swab screening with polymerase chain reaction (PCR) testing for influenza. Adjusted analysis showed a 38% reduction in influenza-related hospitalisations in vaccinated vs unvaccinated individuals. Influenza-positive patients experienced higher crude mortality (9.7% vs 7.9%; p=0.047) and critical illness (17.2% vs 12.1%; p<0.001) than influenza-negative patients. Risk factors for mortality in influenza-positive patients included age >75 years, cardiac comorbidity, residence in long-term care, and home oxygen use.

Comment: The World Health Organization recommends the influenza vaccine for patients with chronic disorders, including COPD, as they are at higher risk of flu-related complications. Most COPD exacerbations are induced by viral respiratory tract infections. Vaccination against influenza could potentially reduce the risk of hospitalisation and mortality resulting from flu-related exacerbations. This Canadian study utilised data from the Serious Outcomes Surveillance Network of the Canadian Immunization Research Network. It included 4198 hospitalised COPD patients with known vaccination status over four winter seasons, analysing nasopharyngeal swabs to diagnose the flu. It highlighted that influenza vaccine was associated with a 38% reduction in influenza-related hospitalisations amongst COPD patients, albeit only 66.5% of COPD patients were vaccinated. COPD patients should receive the influenza vaccine on an annual basis as a protective measure against influenza and associated adverse health consequences.

Reference: Chest 2019;155(1):69-78
Abstract

Vitamin D to prevent exacerbations of COPD

Authors: Jolliffe D et al.

Summary: This systematic review and meta-analysis of individual participant data from randomised controlled trials (RCTs) determined the impact of vitamin D supplementation on COPD exacerbations. A search of PubMed, Embase, the Cochrane Central Register of Controlled Trials and Web of Science identified 3 RCTs of vitamin D supplementation in a total of 469 patients with COPD that were suitable for inclusion. Meta-analysis of individual participant data showed that vitamin D supplementation did not influence the overall rate of moderate to severe COPD exacerbations. However, prespecified subgroup analysis revealed that protective effects were seen in participants with baseline 25-hydroxyvitamin D levels <25 nmol/L but not baseline levels ≥25 nmol/L.

Comment: It is postulated that the protective effects of vitamin D against respiratory tract infections and consequential COPD exacerbations are mediated by a common mechanism which involves induction of antiviral and antimicrobial responses. This meta-analysis found oral vitamin D supplements reduced moderate to severe COPD exacerbations in patients with low circulating levels of 25-hydroxyvitamin D metabolite at baseline. However, no protective effect was noted for patients with normal 25-hydroxyvitamin D levels (≥25 nmol/L) prior to supplementation. Identifying COPD patients with low vitamin D levels could be an effective strategy to reduce exacerbations and improve clinical outcomes by oral vitamin D supplementation.

Reference: Thorax 2019;74:337-45
Abstract

Serum levels of hyaluronic acid are associated with COPD severity and predict survival

Authors: Papakonstantinou E et al.

Summary: This study investigated whether hyaluronic acid (HA) and its degrading enzyme hyaluronidase (HYAL)-1 are associated with COPD severity and outcome. Serum HA levels were assessed in a discovery cohort of 80 COPD patients at stable state and during an exacerbation. HA, HYAL-1 and HYAL-1 enzymatic activity were also evaluated at stable state, during an exacerbation and 4 weeks after an exacerbation in 638 COPD patients from the PROMISE validation cohort. In the discovery cohort, serum HA levels were higher during exacerbations than when stable. In the validation cohort, HA was higher during moderate and severe exacerbations than at baseline, and remained higher after 4 weeks. HA was independently associated with time to death and was therefore strongly predictive of overall survival. Serum HYAL-1 was increased during moderate and severe exacerbations, but decreased after 4 weeks. HYAL-1 enzymatic activity at stable state was inversely correlated with FEV_1 (% predicted) and survival time.

Comment: Acute COPD exacerbations are associated with pro-inflammatory degradation of HA. HA degradation may contribute to airway inflammation and subsequent lung function decline during exacerbations. This study revealed high levels of serum HA were associated with COPD exacerbations and were predictive of the overall survival rate. HA and related degradation products could serve as potential targets in controlling airway inflammation and remodelling in COPD.

Reference: Eur Respir J 2019;53(3):1801183
Abstract

Efficacy of aclidinium/formoterol 400/12 µg, analyzed by airflow obstruction severity, age, sex, and exacerbation history

Authors: D'Urzo A et al.

Summary: This pooled analysis of the ACLIFORM and AUGMENT studies evaluated the efficacy of aclidinium/formoterol in various subgroups (airflow obstruction severity, age, sex, and exacerbation history). In the 2 studies, 3394 patients with COPD were randomised to receive aclidinium/formoterol 400/12µg, aclidinium or formoterol monotherapy, or placebo twice daily for 24 weeks. Patients were then analysed according to baseline airflow obstruction severity (moderate vs severe), age (<65 vs ≥65 years), sex, and exacerbation history (0 vs ≥1 exacerbation in the previous 12 months). Aclidinium/formoterol improved post-dose FEV_1 vs placebo and monotherapy in all subgroups, and trough FEV_1 vs placebo and formoterol across all subgroups. Improvements in trough FEV_1 were observed vs aclidinium in patients with severe airflow obstruction, patients aged <65 years, males, and patients with exacerbation history. Improvements in dyspnoea were observed vs placebo in all subgroups, and vs monotherapies for patients with moderate (formoterol) or severe airflow obstruction (aclidinium), patients aged <65 years, males (formoterol), and patients with no exacerbation history (formoterol).

Comment: Long acting bronchodilators are the cornerstone treatment in COPD. With demonstrated efficacy and good safety profile of fixed-dose combination LAMA/LABA therapies, current COPD guidelines are advocating the use of LAMA/LABA dual bronchodilation therapy to maximise bronchodilation prior to ICS introduction. This study showed aclidinium (LAMA) and formoterol (LABA) combination therapy, when compared with the monotherapy constituents, was superior in reducing the risk of exacerbation/dyspnoea burden and improving lung function. Of note, aclidinium/formoterol is administered in a twice daily manner. Twice daily administration of aclidinium/formoterol has been shown to improve early morning and nocturnal symptoms in COPD. Twice daily dosing is not associated with lower treatment adherence when compared with once daily treatment regimens and may be preferred by COPD patients with significant nocturnal symptom burden.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:479-91
Abstract

Long-term cost-effectiveness of the fixed-dose combination of tiotropium plus olodaterol based on the DYNAGITO trial results

Authors: Hoogendoorn M et al.

Summary: This study estimated the cost-effectiveness of the fixed-dose combination tiotropium/olodaterol vs tiotropium monotherapy in COPD patients in the French setting. A COPD patient-level simulation model was used to simulate the lifetime effects and costs for 15,000 patients receiving either tiotropium/olodaterol or tiotropium monotherapy, based on findings from the DYNAGITO trial. The number of quality-adjusted life-years (QALYs) was 0.042 higher for treatment with tiotropium/olodaterol vs tiotropium monotherapy. From a societal perspective, tiotropium/olodaterol resulted in a cost increase of €123 and an incremental cost-effectiveness ratio (ICER) of €2900 per QALY compared with tiotropium monotherapy. From a French National Sickness Fund perspective, total lifetime costs were reduced by €272 with tiotropium/olodaterol.

Comment: COPD is a leading global health issue. The direct and indirect COPD-related costs amounted to 36 billion US dollars in 2010. COPD exacerbations account for the majority of costs in COPD management. Combining bronchodilators with different mechanisms/durations of action may optimise bronchodilation in a synergistic manner. Significant advantages include reduction of COPD exacerbation and improvement of lung function. It also has a lower risk of adverse effects when compared with increasing the dose of a bronchodilator monotherapy. This population study highlighted that duo bronchodilatation therapy with tiotropium (LAMA) and olodaterol (LAMA) was a cost-effective measure with reduced total lifetime costs when compared with tiotropium monotherapy. Tiotropium/olodaterol combination therapy has been demonstrated to improve COPD symptoms and patient-reported outcomes beyond tiotropium. It is also superior to ICS/LABA combination (salmeterol/fluticasone) in improving lung function for patients with moderate to severe COPD.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:447-56
Abstract

Real-life effectiveness of indacaterol-glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD

Authors: Kaplan A et al.

Summary: The POWER study investigated the effectiveness of indacaterol/glycopyrronium in patients with symptomatic COPD after switching from tiotropium or salmeterol/fluticasone therapy. Patients with moderate to severe COPD who were symptomatic despite taking tiotropium 18µg once daily or salmeterol/fluticasone twice daily were switched to treatment with open-label indacaterol/glycopyrronium 110/50µg once daily for 16 weeks. Trough FEV_1 improved by 175ml at week 16 (176ml in those who switched from tiotropium and 172ml in those who switched from salmeterol/fluticasone). Significant improvements were observed at week 16 in mean transition dyspnoea index scores and COPD assessment test scores.

Comment: The mainstay of pharmacological treatment in COPD rests with long-acting bronchodilators with the therapeutic aim of relieving symptoms and preventing exacerbations. This prospective cohort study showed that switching from LAMA monotherapy or LABA/ICS to LAMA/LABA combination therapy had a favourable effect on lung function and patient reported outcomes in symptomatic moderate to severe COPD patients. Previous studies demonstrated that combination long-acting bronchodilator therapy is more effective than long-acting bronchodilator monotherapy in preventing COPD exacerbations in patients with a known history of exacerbations. Most importantly, LABA/LAMA combination therapy has been shown to reduce COPD exacerbations to a greater degree than ICS/LABA combination therapy.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:249-60
Abstract

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