Making Education Easy

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Abbreviations used in this issue:

BMI = body mass index; **COPD** = chronic obstructive pulmonary disease; **FEV_1** = forced expiratory volume in 1 s; **GOLD** = Global Initiative for Chronic Obstructive Lung Disease; **HR** = hazard ratio; **ICS** = inhaled corticosteroid; **LABA** = long-acting beta-agonist; **LAMA** = long-acting muscarinic antagonist; **PR** = pulmonary rehabilitation.

Welcome to the latest issue of COPD Research Review.

In this issue, an analysis of the CanCOLD study finds that poor sleep quality increases the risk of future COPD exacerbations, a Canadian study highlights opportunities for earlier diagnosis of COPD, and UK researchers suggest that long-term ICS therapy at a dose ≥500 µg/day (fluticasone equivalents) is associated with an increased risk of diabetes, diabetes progression, and osteoporosis in COPD patients. A meta-analysis supports the obesity paradox in COPD, a Swedish population study finds that triple therapy with ICS/LABA/LAMA is still the most common treatment combination for COPD in that country (contrary to current guidelines), and we finish with two studies of pulmonary rehabilitation in patients with COPD.

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

Kind Regards,

Dr Philip Lee

philip.lee@researchreview.com.au

Impaired sleep quality in COPD is associated with exacerbations

Authors: Shorofsky M et al., for the CanCOLD Collaborative Research Group

Summary: This analysis of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study evaluated the relationship between subjective sleep quality and risk of COPD exacerbations. 480 patients with COPD who had completed 18 months of follow-up in the CanCOLD study were included. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI); 203 patients had poor sleep quality at baseline (PSQI score >5). Those with COPD exacerbations during follow-up had higher median baseline PSQI scores (6.0 vs 5.0; p=0.01) and were more likely to have baseline PSQI scores >5 (50.3% vs 37.3%; p=0.01) than those without exacerbations during follow-up. Time to COPD exacerbation was shorter in patients with poor sleep quality (adjusted HR, 1.49).

Comment: Previous studies have demonstrated that poor sleep quality in COPD is associated with reduced health-related quality of life and reduced daytime physical activity. This prospective population-based longitudinal study utilised data from the CanCOLD study and demonstrated that poor subjective sleep quality was associated with consequential symptomatic COPD exacerbations. A plausible mechanism is that sleep disruption could impede immune function and increase systemic inflammation, resulting in worsening COPD control and increasing the risk of COPD exacerbation. Adequate treatment for sleep-disordered breathing could improve the outcome of COPD and potentially reduce the risk of exacerbation.

Reference: Chest 2019;156(5):852-63
Abstract

Healthcare system encounters before COPD diagnosis

Authors: Johnson K et al.

Summary: This registry-based longitudinal cohort study determined the frequency of healthcare system encounters before COPD diagnosis in patients in British Columbia, Canada, in 1996–2015. Analysis of administrative health data for 112,635 COPD patients showed that, in the 5 years before diagnosis, patients with COPD interacted frequently with pharmacists (mean 14.09 visits/year), primary care physicians (mean 10.29 visits/year) and specialists (mean 8.11 visits/year). In the 2 years prior to diagnosis, 72.1% of patients had a respiratory-related primary care visit that did not result in a COPD diagnosis. Compared with non-COPD individuals, patients with COPD had higher rates of encounters with primary care physicians (rate ratio [RR], 1.40), specialists (RR, 1.35) and pharmacists (RR, 1.62).

Comment: COPD is underdiagnosed and often misdiagnosed, leading to a delayed diagnosis and a significant impact on prognosis and healthcare utilisation. This Canadian study showed COPD patients have a higher utilisation rate of outpatient services, including primary care, specialist and pharmacist encounters. Early accurate diagnosis of COPD enables prompt implementation of interventions, including smoking cessation, exercise and rehabilitation, as well as instituting appropriate pharmacotherapy to improve patient outcomes. Early diagnosis of COPD can be achieved by targeted case finding to identify appropriate candidates for diagnostic confirmatory spirometry.

Reference: Thorax 2019; published online Nov 8
Abstract

Exacerbation action plans for patients with COPD and comorbidities

Authors: Lenferink A et al.

Summary: This international randomised controlled trial evaluated the impact of an exacerbation action plan on the number of COPD exacerbations. 201 COPD patients (GOLD stages 2–4) with ≥1 comorbidity (ischaemic heart disease, heart failure, diabetes, anxiety, depression) were randomised to a patient-tailored self-management intervention or usual care. Daily symptom diaries were completed for 12 months. The primary outcome (COPD exacerbation days per patient per year) did not differ significantly between groups (median 9.6 vs 15.6; p=NS). However, the duration of each exacerbation was shorter in the self-management group (median 8.1 vs 9.5 days; p=0.021), and the probability of having ≥1 respiratory-related hospitalisation was lower (relative risk, 0.55; p=0.008). No between-group differences were seen for all-cause hospitalisations or mortality.

Comment: Multiple comorbidities, including cardiovascular diseases, osteoporosis, depression/anxiety, skeletal muscle dysfunction, metabolic syndrome and lung cancer frequently co-exist in COPD patients. COPD exacerbations negatively impact on mortality and increase the risk of hospitalisation, especially in patients with multiple comorbidities. It has been advocated that COPD patients with significant burden of comorbidities should be trained to use a patient-tailored multi-disease exacerbation action plan. Although this international randomised controlled trial was negative for the intended primary outcome (no statistically significant reduction in the number of COPD exacerbation days), there was a significant reduction of COPD exacerbation duration and the risk of respiratory-related hospitalisations. This study has demonstrated that implementation of a self-management plan for COPD is a safe and effective strategy. It should be directed at addressing exacerbations and optimising management of concomitant chronic diseases in COPD patients.

Reference: Eur Respir J 2019;54(5):1802134
Abstract

Inhaled corticosteroids in COPD and onset of type 2 diabetes and osteoporosis

Authors: Price D et al.

Summary: This matched cohort study investigated the impact of ICS treatment on the onset of type 2 diabetes or osteoporosis in patients with COPD. Data were retrieved from 2 large UK databases (1983–2016) for patients aged ≥40 years who initiated ICS or long-acting bronchodilator (LABD) therapy for COPD. Three study cohorts were used to determine the relationship between ICS treatment and diabetes onset (n=17,970), diabetes progression (n=804), and osteoporosis onset (n=19,898). Median follow-up was 3.7–5.6 years per treatment group. For patients taking ICS compared with LABD, the risk of diabetes onset was significantly increased (adjusted HR, 1.27), but there was no overall increase in risk of diabetes progression or osteoporosis onset. However, the risks of diabetes onset, diabetes progression, and osteoporosis onset were all significantly increased at mean ICS dosages ≥500 µg/day vs <250 µg/day (fluticasone propionate-equivalent).

Comment: Long-term ICS use in COPD is associated with important risks, including type 2 diabetes and osteoporosis. Observational studies have linked ICS use to an increased risk of developing diabetes and poor glycaemic control in patients with known diabetes. This matched cohort study showed significantly higher risk for diabetes onset in COPD patients with long-term ICS use. Of concern, a probable dose-response relationship exists between ICS use and onset of diabetes/osteoporosis. COPD patients receiving mean daily exposure of ICS dose ≥500 µg/day of fluticasone propionate-equivalent have significantly higher risk of diabetes onset/progression and osteoporosis onset when compared to patients receiving <250 µg/day. High-quality clinical trials have demonstrated important health risks associated with long-term ICS in COPD, and vigilant use is advocated.

Reference: NPJ Prim Care Respir Med 2019;29(1):38
Abstract

Treatment failure and hospital readmissions in severe COPD exacerbations treated with azithromycin versus placebo – a *post-hoc* analysis of the BACE randomized controlled trial

Authors: Vermeersch K et al., on behalf of the BACE trial investigators

Summary: The BACE trial investigated the efficacy of long-term low-dose azithromycin in patients hospitalised with infective COPD. This *post-hoc* analysis of the trial determined the impact of azithromycin on hospital readmissions, and identified which clinical subgroups were most likely to benefit. In the BACE trial, treatment failure was defined as a composite of treatment intensification with medication, step-up in hospital care, readmission for respiratory reasons, or all-cause mortality. Compared with placebo, low-dose azithromycin (250mg every 2 days) was associated with a 24% decrease in treatment failure rates over the 3-month treatment period, mainly due to a 50% reduction in step-up in hospital care, and a 53% reduction in hospital readmissions. Subgroup analysis showed that azithromycin significantly reduced hospital readmissions in patients with high C-reactive protein (CRP; >50 mg/L) or low blood eosinophil count (<300 cells/µL) upon admission.

Comment: Azithromycin confers anti-inflammatory benefits and has been proven to reduce the risk of exacerbation in COPD. However, clinical application is hindered by potential side effects, including ototoxicity and probable antibiotic resistance. This Belgian study showed that low-dose azithromycin is effective in preventing subsequent hospital readmissions within 3 months of first hospital presentation in COPD patients with infective exacerbation necessitating hospitalisation. High CRP (>50 mg/L) or low blood eosinophil count (<300 cells/µL) may identify the appropriate subgroup of COPD and guide azithromycin therapy.

Reference: Respir Res 2019;20(1):237
Abstract

BMI is associated with FEV_1 decline in chronic obstructive pulmonary disease

Authors: Sun Y et al.

Summary: This meta-analysis determined the relationship between BMI and the rate of FEV_1 decline in COPD patients. A search of various databases identified 4 randomised controlled trials that reported an association between BMI and FEV_1 decline in COPD patients that were suitable for inclusion. Meta-analysis of the data found that the estimated rate of FEV_1 decline decreased with increasing BMI.

Comment: Previous studies have demonstrated that overweight is associated with a lower risk of all-cause mortality amongst COPD patients whilst underweight is associated with a higher risk of all-cause mortality. Lower BMI is also more prevalent in severe COPD stages and is associated with worse prognosis and survival. This systematic review showed a low BMI is a risk factor for accelerated lung function decline, whilst high BMI has a protective effect. The paradoxical relationship between obesity and high BMI in COPD is an important treatment focus as previous research has demonstrated that dietary energy restriction and resistance strength training result in significant improvements in BMI, exercise tolerance and health status, whilst preserving skeletal muscle mass with improvement of prognostic score.

Reference: Respir Res 2019; published online Oct 29
Abstract

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.

Global prevalence of asthma-COPD overlap (ACO) in the general population

Authors: Hosseini M et al.

Summary: This systematic review and meta-analysis estimated the prevalence of asthma-COPD overlap syndrome (ACOS) in the general population. A search of ISI Web of Knowledge, MEDLINE/PubMed, and Scopus identified 27 studies that were suitable for inclusion. The pooled prevalence of ACOS was 2.0% in the general population, 26.5% among patients with asthma, and 29.6% among patients with COPD. The global prevalence of asthma-only was 6.2% and the global prevalence of COPD-only was 4.9%.

Comment: ACOS is a term applied to patients with clinical features of both asthma and COPD. It has a wide array of definitions and the exact prevalence is difficult to determine. This meta-analysis estimated the global ACOS prevalence based on population-based studies and concluded that about 2.0% of the general population is affected by ACOS. However, the diagnostic criteria of ACOS will strongly influence the estimated prevalence. As ACOS is associated with worse morbidity than asthma and COPD alone, a unified and universally accepted definition is necessary. The current recommendations for treatment in ACOS suggest an initial therapy of long-acting bronchodilators and an ICS. Research on application of biologic therapies is limited as most trials have excluded ACOS patients.

Reference: Respir Res 2019; published online Oct 23
Abstract

A cross-sectional study assessing appropriateness of inhaled corticosteroid treatment in primary and secondary care patients with COPD in Sweden

Authors: Sulku J et al.

Summary: This study used an algorithm proposed by the International Primary Care Respiratory Group (IPCRG) to evaluate the appropriateness of ICS treatment in a Swedish cohort of 561 primary and secondary care patients with COPD. Triple therapy (ICS/LABA/LAMA) was found to be the most common treatment combination (46% of patients), and 63% of patients were using ICS. Application of the IPCRG algorithm found a possible indication for discontinuing ICS treatment in 55% of patients, and for starting ICS treatment in 18% of patients. The strongest factors associated with ICS therapy were frequent exacerbations, secondary care contacts, and very severe airflow limitation.

Comment: Previous study has demonstrated that ICS overuse is common amongst early COPD patients and is not supported by current guidelines. This Swedish population study highlighted an alarming phenomenon – triple agents (ICS/LABA/LAMA) remained the most common treatment combination, used by nearly half of the study population with an overall 63% of patients on ICS therapy. Of note, 55% of COPD patients on ICS met the criteria for which ICS withdrawal could be expedited. There are multiple health risks associated with using ICS long term in COPD patients. There are currently no guidelines on the best approach for withdrawing from ICS treatment. Consultation with a respiratory specialist is advocated when planning ICS withdrawal in COPD patients who are unlikely to benefit from ICS.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:2451-60
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.

Influence of socioeconomic deprivation on short- and long-term outcomes of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease

Authors: Grosbois J et al.

Summary: This retrospective observational study investigated the impact of socioeconomic deprivation on PR outcomes in patients with COPD. 459 patients undergoing home-based PR were divided into 2 groups according to whether or not they were socially deprived. The PR programme involved an individualised plan of retraining exercises, physical activities, therapeutic education, and psychosocial and motivational support, and was performed at home once a week for 8 weeks. Exercise tolerance, anxiety and depression, and quality of life were assessed using the 6 min stepper test (6MST), Hospital Anxiety and Depression Scale (HADS), and Visual Simplified Respiratory Questionnaire (VSRQ). Patients were assessed before the PR programme (baseline) and then at 2 (T2), 8 (T8), and 14 (T14) months after baseline. At baseline, 6MST, VSRQ, and HADS measures were lower in the socially deprived group than the non-socially deprived group. However, there were no significant between-group differences in any outcomes at T2, T8, and T14.

Comment: PR programmes are effective in improving the functional and psychological state of symptomatic COPD patients. However, socioeconomic deprivation might potentially limit access to PR and lead to worse clinical outcomes. This French retrospective study demonstrated that a home-based PR programme was effective in improving the functional and psychological outcomes of COPD patients, with no significant differences amongst patients with varying socioprofessional status. Regular physical activity is recommended for all patients with COPD, including normal daily activity as well as formal programmes such as PR. The benefits of PR have been demonstrated from inpatient, outpatient and home settings.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:2441-9
Abstract

Benefits of different intensities of pulmonary rehabilitation for patients with moderate-to-severe COPD according to the GOLD stage

Authors: He G et al.

Summary: This study investigated the appropriate intensity of PR exercise training for patients with moderate-to-severe COPD. Patients were randomised to 1 of 3 different PR intensities (low-, moderate-, and high-intensity) for 20 weeks. For patients with moderate COPD, all measured parameters improved significantly in the moderate- and high-intensity PR groups ($p<0.01$), but the frequency of acute exacerbations and the modified Medical Research Council Dyspnea Scale score did not improve in the low-intensity PR group. For patients with severe COPD, all variables improved in the high-intensity PR group ($p<0.05$), although improvements were less than those seen in patients with moderate COPD.

Comment: Patients at all stages of COPD benefit from PR and maintenance of physical activity, in the domains of exercise tolerance and improving symptoms of dyspnoea and fatigue. This Chinese study supports the application of high-intensity PR in selected patients with higher levels of improvement in severe COPD patients. Exercise training is the key component of PR and a high intensity that focuses on endurance exercises of the leg muscles through walking, exercise circuits and stationary cycling is advocated. The current minimum length of an effective rehabilitation programme is typically 6 weeks. The longer the programme continues, the more likely it is that robust results could be derived.

Reference: Int J Chron Obstruct Pulmon Dis 2019;14:2291-2304
Abstract

