Welcome to the latest issue of COPD Research Review.

In this issue, a feasibility study finds that a metered cryospray delivered to the tracheobronchial tree is safe and associated with clinically meaningful improvements in COPD, the ARCTIC study reports the impact of inhaled corticosteroids on fracture risk and osteoporosis in COPD patients, and an analysis of data from the ECLIPSE study identifies patients most at-risk of early AECOPD recurrence. Also in this issue, Spanish researchers report that people with asthma and COPD are likely to have greater work absenteeism than the general population, and a palliative care study compares end-of-life practices in patients with COPD versus lung cancer.

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

Kind Regards,
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A prospective safety and feasibility study of metered cryospray for patients with chronic bronchitis in COPD

Authors: Garner JL et al.

Summary: This study evaluated the feasibility, efficacy and safety of a metered cryospray in COPD patients with chronic bronchitis. 35 patients aged 47–76 years with COPD (GOLD stages 1–3) underwent staggered liquid nitrogen treatments via metered cryospray to the tracheobronchial tree. 34 patients completed 3 treatments (each lasting a mean 34.3 min) at intervals of 4–6 weeks. Clinically meaningful improvements in patient-reported outcomes (assessed by SGRQ, COPD Assessment Test [CAT], and Leicester Cough Questionnaire [LCQ]) were observed at 3 months. Changes in CAT were durable to 6 months, while changes in SGRQ and LCQ were durable to 9 months. At 12 months, 14 serious adverse events had been reported in 11 patients. Nine of these were respiratory-related but none of them were device- or procedure-related adverse events.

Comment: Mucus hypersecretion is a poor prognostic factor in COPD. This study reports on metered cryospray, a novel approach to treating epithelial cell metaplasia and goblet cell hyperplasia where gaseous liquid nitrogen is sprayed onto the airways via bronchoscopy – in theory, causing ablation and regeneration of the epithelium without affecting the underlying extracellular matrix. There was a sustained improvement in quality of life scores (most notably the SGRQ impact domain and LCQ) that exceeded the minimum clinically important difference over 9 months. Since this was a small, uncontrolled feasibility study, the conclusions we can draw are limited – indeed, mucosal biopsies taken in a subset of patients did not show any observable differences to provide objective, histological support for the patient-report outcomes. However, if the results are replicated in a controlled (sham treatment) study design, metered cryospray may prove to be an exciting new treatment in COPD.

Reference: Eur Respir J 2020; published online Dec 17

Abstract
Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients

Authors: Janson C et al.

Summary: The ARCTIC study evaluated the impact of ICS use on osteoporosis and fracture risk in patients with COPD. Electronic medical record data linked to National Health Registries were collected for 9651 COPD patients and 59,454 matched controls at 52 Swedish primary care centres from 2000 to 2014. During follow-up, 19.9% of COPD patients and 12.9% of controls had ≥1 osteoporosis-related event (any fracture, fracture typically related to osteoporosis, prescription of drugs for osteoporosis, and diagnosis of osteoporosis; p<0.0001). Multivariate analysis of the COPD group showed that ICS treatment had a dose-effect relationship, with the risk of any osteoporosis-related event being higher for high-dose ICS (risk ratio 1.52, 95% CI 1.24–1.62) than low-dose ICS (risk ratio 1.27, 95% CI 1.13–1.56) when compared with COPD patients not using ICS.

Comment: Unlike their association with the increased risk of pneumonia, the potential systemic side-effects of ICS in COPD are less well recognised. In particular, there is conflicting data on the risk of osteoporosis and associated bone fracture with ICS use. In this real-world health registry study from Sweden, the investigators found that ICS prescription was associated with an increased risk of osteoporosis and fractures typically associated with osteoporosis, with an apparent dose-dependent effect. This is yet another reminder for clinicians that ICS, particularly higher doses, are not without side-effects. In COPD patients, their prescription should be limited to those who may derive the greatest benefit (i.e. patients who continue to experience exacerbations despite combination LABA/LAMA therapy, and possibly those with peripheral blood eosinophilia).

Reference: Eur Respir J 2021; published online Feb 17

Interstitial lung abnormalities and the clinical course in patients with COPD

Authors: Lee TS et al.

Summary: This retrospective study evaluated the clinical course of COPD according to the presence and progression of interstitial lung abnormalities (ILAs). 363 COPD patients were evaluated for radiological findings on chest CT, history of AECOPD, and lung function changes during longitudinal follow-up. 44 patients had equivocal ILAs and 103 had definite ILAs. Patients with ILAs were older and had lower FEV1 and FVC than those without ILAs. During a mean follow-up of 5.2 years, patients with ILAs had a higher annual incidence of moderate to severe AECOPD (p=0.002) and a higher risk of frequent exacerbation (p=0.045) than patients without ILAs. Patients with progressive ILAs had a higher rate of annual decline in FEV1 and FVC than those with improved or no change in ILAs.

Comment: There has been a lot of interest in the significance of ILAs (minor parenchymal changes observed on thoracic CT) as markers of subclinical pathology. In COPD, ILAs have been associated with worse quality of life and mortality. In this cohort of 363 COPD patients, 40% had measurable ILAs; their presence was a predictor of the rate of moderate/severe acute exacerbations, independent of other known predictors such as age, FEV1, and smoking intensity. COPD patients with ILAs were twice as likely to be frequent exacerbators (≥2 per year) than those without. Interestingly, the 27% of patients in whom the ILAs progressed during follow-up had greater decline in FEV1. These data suggest that, far from being a benign finding, the presence of ILAs in COPD may be a marker of higher disease activity associated with worse clinical outcomes.

Reference: Chest 2021;159(1):128-37
Computed tomography-based airway surface area-to-volume ratio for phenotyping airway remodeling in chronic obstructive pulmonary disease

Authors: Bodduluri S et al.

Summary: This study used chest CT-based airway surface area-to-volume ratio (SA/V) to phenotype airway remodelling in COPD. 4325 patients with COPD (GOLD stages 0–4) and 73 non-smokers who were part of the COPDGene cohort were included. Multivariable regression analyses showed that SA/V of the subtracheal airway tree was independently associated with FEV₁/FVC, FEV₁% predicted, 6-minute walk distance, respiratory quality of life, and lung function decline. Patients with predominant airway loss had worse survival than those with predominant airway narrowing (adjusted HR 1.58, 95% CI 1.18–2.13; p=0.002).

Comment: Loss of airway volume may be due to airway luminal narrowing and/or airway loss. This CT imaging study measured the airway SA/V of 4325 individuals in the COPDGene study. The theoretical basis of this metric is that airway narrowing will cause greater reduction in V relative to SA and hence a positive AS/A,V, whereas airway loss will cause greater reduction in SA relative to V and hence a negative AS/A,V. The investigators were able to categorise participants into predominantly ‘airway narrowing’ or ‘airway loss’ groups based on CT changes over 5 years; the predominantly airway loss group had significantly faster FEV₁ decline (mean 46 vs 38 ml/year) and higher all-cause mortality (HR 1.58). Although it requires replication in other studies and histological confirmation, changes in airway SA/V ratio may become an important tool in dissecting the heterogeneity of longitudinal outcomes in COPD.

Reference: Am J Respir Crit Care Med 2021;203(2):185–91

Deterioration of nighttime respiratory mechanics in COPD: Impact of bronchodilator therapy

Authors: Domnik NJ et al.

Summary: This randomised crossover trial investigated the impact of dual, long-acting bronchodilator on nocturnal respiratory mechanics in patients with COPD. 20 patients with COPD (moderate/severe airway obstruction and lung hyperinflation) underwent serial measurements of inspiratory capacity (IC), spirometry, breathing pattern, oesophageal and transdiaphragmatic pressures, and diaphragm electromyography for 12h after an evening dose of long-acting bronchodilator (aclicinium bromide/formoterol fumarate dihydrate 400/12μg) or placebo. Compared with placebo, evening bronchodilation did not improve morning trough IC, but did improve nadir IC, peak IC, area under the curve for 12h after the dose, and IC at 10h after the dose (p<0.05). Total airways resistance, lung hyperinflation, inspiratory neural drive, and tidal oesophageal and transdiaphragmatic pressures also improved after the bronchodilator dose (p<0.05 vs placebo) with no change in ventilation or breathing pattern.

Comment: In many ways, sleep can be considered a ‘stress test’ for the respiratory system. Changes in respiratory mechanics (particularly dynamic hyperinflation) during sleep might contribute to nocturnal symptoms, poor sleep quality, and poor quality of life in COPD. In this study, an evening dose of combination long-acting bronchodilator in hyperinflated COPD patients increased IC, reduced tidal respiratory effort, and reduced neuromechanical dissociation when measured at various intervals overnight compared to placebo — effects which were probably due to more efficient inspiratory muscle function rather than changes in central chemoreceptor outflow. Although the primary outcome (change in morning trough IC) and overnight polysomnographic parameters were no different between bronchodilator and placebo groups, this study suggests that optimising breathing mechanics may be important not just for exercise but also for sleep. Whether this translates into improved outcomes for COPD patients requires further testing.


Should the number of acute exacerbations in the previous year be used to guide treatments in COPD?

Authors: Sadatsafavi M et al.

Summary: This study analysed data from two large cohorts (ECLIPSE and SPIROMICS) to evaluate the stability of the frequent exacerbator phenotype. In both cohorts, the pattern of AECOPD supported the presence of an underlying AECOPD rate that is stable over time. However, the observed AECOPD rate varied markedly year-to-year in some patients. For patients with an underlying rate of 0.8–3.1 events per year (frequent exacerbators), rates of AECOPD changed more than 30% of the time over 2 consecutive years due to chance alone. This value increased to more than 45% for those with an underlying rate of 1.2–2.2 events per year.

Comment: The conventional dogma is that past exacerbations predict future exacerbation risk in COPD. However, the ‘frequent exacerbator’ (≥2 events per year) phenotype may only be a useful predictor of future exacerbation risk if that phenotype remains stable over time (as suggested by the ECLIPSE study). In this complex modelling study, the investigators conclude that a stable frequent exacerbator phenotype likely does exist, and that patients with the lowest and highest underlying rates of AECOPD are most likely to remain stable within their respective classifications. Where it becomes more difficult is when a patient’s exacerbation rate moves from infrequent to frequent in any given year – is this a result of random variation, or of deteriorating clinical state? The authors argue that, despite the apparent stability of the ‘frequent exacerbator’ phenotype, more detailed individual-level data should be incorporated into future predictive models.

Reference: Eur Respir J 2021; published online Feb 11

Predicting re-exacerbation timing and understanding prolonged exacerbations

Authors: Meeraus WH et al.

Summary: This analysis of data from the ECLIPSE cohort determined risk factors for re-exacerbations and prolonged AECOPD. 1420 patients with COPD who were followed up for 180 days after first exacerbation (index date) were included. More patients experienced early (30.9%) than late (18.7%) re-exacerbations, but 50.4% of patients had no re-exacerbation within 180 days. Predictors of re-exacerbation risk within 180 days included lower post-bronchodilator FEV₁, a higher number of moderate/severe exacerbations on or before the index date, higher SGRQ total score, and the season of index exacerbation (autumn vs winter). The median duration of moderate/severe AECOPD was 12 days; 22.7% of patients had a prolonged AECOPD. The odds of experiencing a prolonged AECOPD were greater for severe vs moderate AECOPD (adjusted OR 1.917; p=0.002) and lower for spring vs winter AECOPD (adjusted OR 0.578, p=0.017).

Comment: Continuing with the theme of exacerbation frequency, clinicians will recognise that select patients experience very frequent exacerbations often only weeks apart. The ability to identify patients most at-risk of this early recurrence may be useful. This re-analysis of the ECLIPSE cohort examined the predictors of ‘early’ (1–90 days) and ‘late’ (91–180 days) re-exacerbation. Approximately half of the 1420 participants experienced a new exacerbation within 180 days of their index exacerbation; of these, more than half were considered ‘early’ re-exacerbations. Independent predictors of early re-exacerbation were lower FEV₁, higher symptom burden (SGRQ), and the number of moderate/severe exacerbations prior to the index exacerbation. This study emphasises that exacerbation history is dynamic, and that once again a dichotomous frequent vs non-frequent (≥2 or <2 per year) exacerbator phenotype is probably not adequate for risk mitigation.


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Cognitive function following pulmonary rehabilitation and post-discharge recovery from exacerbation in people with COPD

Authors: France G et al.

Summary: This 6-week prospective study evaluated the recovery of cognition following AECOPD, and the impact of PR on cognitive impairment. 67 patients with stable COPD who completed PR (PR group) and 45 patients with AECOPD (AECOPD group) were assessed for cognitive function (Montreal Cognitive Assessment [MoCA]), health status (COPD Assessment Test, Chronic Respiratory Questionnaire), lower extremity function (Short Physical Performance Battery), and psychological well-being (Hospital Anxiety and Depression Score). Follow-up assessments were performed after a 6-week recovery post-discharge in the AECOPD group and after PR in the PR group. The AECOPD group showed no improvement in MoCA after a 6-week recovery post-discharge, despite improvements in all other clinical outcomes. PR uptake among the AECOPD group was not associated with the presence of cognitive impairment. Patients in the PR group with cognitive impairment at baseline had a significant improvement in MoCA score after PR (p=0.004).

Comment: This study used the MoCA test to identify participants with cognitive impairment (MoCA score <26). It reaffirmed the high prevalence of cognitive impairment in the COPD population. Additionally, there were two important conclusions: 1) cognitive impairment does not appear to be a barrier to PR uptake or completion; 2) stable COPD patients with cognitive impairment had a significant improvement in cognition following PR. The latter finding may be important for maintaining independence and self-efficacy in people with COPD. This is further evidence of the multi-dimensional benefits of PR in COPD despite significant improvements in symptoms and other psychological domains. The short duration of follow-up (6 weeks), small sample size, and lack of a sensitivity analysis by cognitive impairment status, may explain this finding.

Reference: Respir Med 2021;176:106249

Work absence in patients with asthma and/or COPD

Authors: Dierick BJH et al.

Summary: This population-based study evaluated the impact of COPD and asthma on work productivity. 14,383 patients with asthma and/or COPD in the MAJORICA cohort were compared with the general population. Multivariable regression analysis showed that patients with asthma and/or COPD had more work absence than the general population (15.2% vs 8.9%; p<0.0001). Patients with asthma had more periods of work absence than patients with COPD (p=0.0001), but the number of days absent was lower in asthma versus COPD patients (median 15 vs 39 days; p<0.001). Patients with asthma–COPD overlap were in between (14.5% had work absence; median duration 27 days).

Comment: Work absenteeism due to chronic disease has important implications for both the individual and society. In this study, the investigators once again showed that people with asthma and COPD have greater work absenteeism than the general population. However, the novelty of this study was in how the data were obtained: in the Balearic Islands region, work absence is only possible through consultation with a GP, who prospectively records the absence and reason for it. This means that measuring work absenteeism does not rely on patient recall. Interestingly, musculoskeletal disorders – not respiratory disease – were the most common cause of work absence even in COPD patients, and anxiety, sleep apnoea and allergic rhinitis were independently associated with any work absence in the asthma/COPD group. This highlights the importance of effective management of these comorbidities in COPD.

Reference: NPJ Prim Care Respir Med 2021; published online Feb 16

Abstract:

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Palliative sedation at the end of life: A comparative study of chronic obstructive pulmonary disease and lung cancer patients

Authors: Tejero E et al.

Summary: This retrospective observational cohort study compared palliative care at the end of life in COPD versus lung cancer patients. 109 patients who died from COPD at a teaching hospital in 2013–2015 were compared with 85 who died from lung cancer. In the last 6 months of life, patients who died from COPD had more hospital admissions due to respiratory causes and less frequent support by a palliative home care team. In addition, during their last hospitalisation, patients who died from COPD had fewer do-not-resuscitate orders and were subjected to more intensive care unit admissions and cardiopulmonary resuscitations. 31% of patients who died from COPD received palliative sedation compared with 53% of those who died from lung cancer (p=0.002).

Comment: This study examined end-of-life care in patients with COPD compared to patients with lung cancer. Not only were COPD patients less likely to be referred to a palliative care service, but they were also less likely to receive palliative sedation during their final hospital admission: COPD was independently negatively associated with palliative sedation (OR 0.48, p=0.02 compared to lung cancer group), while prior use of opiate medications (OR 2.7) and palliative home care team support (OR 4.7) were positive predictors of palliative sedation. COPD patients may have unique palliative care requirements, and individualised care is essential. However, as exemplified by this study, bridging gaps in referral and access is a necessary first step towards providing adequate, effective palliative care for COPD patients.

Reference: Respiration 2020; published online Dec 18

Abstract

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