Respiratory Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue
6MWD = 6-minute walk distance
COPD = chronic obstructive pulmonary disease
ED = emergency department
FEV = forced expiratory volume
ICS = inhaled corticosteroid
LABA = long-acting β-agonist
LAMA = long-acting muscarinic antagonist
NNH/NNT = number needed to harm/treat
QOL = quality of life
RCT = randomised controlled trial
SGRQ = St George's Respiratory Questionnaire

Welcome

to this winter issue of Respiratory Research Review with the topic of COPD (chronic obstructive pulmonary disease). 'Hygge but harmful? Wood-burning stoves under scrutiny' is the title of an editorial by Talha Khan Burki. He details that log burners are 'up there' with the top polluters like industry, coal burning and road transport. He reviews data that wood burning may contribute 38% to the UK emission of particles less than 2.5um (PM25), which is thought to cause about 3500 deaths and 2000 hospital admissions yearly for respiratory conditions in London alone. His colleague, Frank Kelly from King's College, is reviewing 'Urban air quality and health' with the focus on diesel fumes. My home town, Hamburg, has been taken to court by the non-government organisation 'Client Earth' for not providing air quality within EU limits.

'Which doctors are taking care of people with COPD?' is a slight variation of the title of an article from Canada. Ontario, which has a comparable primary healthcare-based system to NZ, has a population of 18 million and about 900,000 have 'doctor-diagnosed COPD'. Of these COPD patients, about 800,000 were seen by their primary-care physician and about 95,000 by a respiratory physician. Respiratory physicians saw just under half of the patients who had two admissions per year. However, about 750,000 saw another specialist, in particular, a cardiologist in 25% of cases. Presumably, the ratios are similar in NZ, that primary care is providing the bulk of COPD care, and also that these patients have a large number of comorbidities, in particular, cardiovascular disease. The interested reader may wish to glance at the article on COPD and heart failure or the editorial on 'the Medusa faces of dyspnoea in COPD'. Also, several esteemed colleagues have published a statement on the vascular involvement in COPD, assisting the development of a differentiated view on this group of patients. Up to 25% of patients with COPD GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 3 and 4 and about 50% of patients undergoing lung volume reduction surgery or lung transplantation have evidence of pulmonary hypertension. Targeted treatment options are minimal at this stage. Finally, Richard Boucher from Chapel Hill wrote a compelling summary of muco-obstructive lung disease. COPD can be dominated by muco-obstructive pathophysiology, which may have more treatment options. At this stage, it is often general practice that provides the 'holistic service for people with advanced disease and chronic breathlessness' – see systematic review and meta-analysis. In this issue, we review an article on a nurse-led service.

Three more links to articles/guidelines address topics my patients have raised during consultations. 1) 'Electronic cigarettes: a task force report from the European Respiratory Society'. It cautions that the long-term effects are unknown and that it may not be any safer than tobacco use in the long term. In this context, the relatively high use during pregnancy raises concerns (MMWR 2019;68:189–94). 2) 'Lung function trajectories in health and disease' is a well-informed personal view by Alvar Agusti and Rosa Faner, providing a review of our current understanding of lung development, natural decline and pathophysiology. 3) 'Mesenchymal stromal cells: a novel therapy for the treatment of chronic obstructive lung disease?' is an in-depth review of their capacity to modify immune responses and enhance tissue report. However, at this stage, we have no evidence of the efficacy in the treatment of COPD.

Thank you for the feedback. We hope you enjoy this selection and for light relief, you may wish to click on 'Should chest CT be part of routine clinical care for COPD?' – 'yes' or 'no'.

Kind regards

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COPD exacerbations: the impact of long versus short courses of oral corticosteroids on mortality and pneumonia

Authors: Sivapalan P et al.

Summary: The impact of the 2014 recommended reduction of oral corticosteroid therapy duration for COPD on 12-month pneumonia hospitalisation risk and all-cause mortality was explored in an observational cohort of 10,152 registry outpatients who experienced an acute COPD exacerbation. Compared with patients who received short-course oral corticosteroid therapy (≤250mg) for their acute COPD exacerbation, those who received a long course (>250mg) had increased likelihoods of pneumonia hospitalisation or all-cause mortality (adjusted hazard ratio 1.3 [95% CI 1.1, 1.4]), pneumonia hospitalisation (1.2 [1.0, 1.3]) and all-cause mortality (1.8 [1.5, 2.2]) over 1 year. Several sensitivity analyses confirmed these findings.

Comment: International guidelines suggest a 5-day course of prednisone for an exacerbation of COPD. The main benefits are that many patients can be managed as outpatients, and the ones admitted have a shorter stay, reduced treatment failure and reduced risk of relapse. However, prednisone comes with the side effects of immunosuppression, increased pneumonia, fluid retention, hypertension, glucose intolerance, loss of muscle strength and others. Pooling data from four Danish registries, these authors compared outcomes between patients who were treated with short versus long courses of prednisone. **Bottom line: shorter courses of prednisone were associated with decreased pneumonia and improved all-cause mortality.**

Reference: BMJ Open Resp Res 2019;6:e000407
Abstract

Health services burden of undiagnosed and overdiagnosed COPD

Authors: Gershon AS et al., for the Canadian Respiratory Research Network

Summary: The health services burden of undiagnosed and overdiagnosed COPD was quantified for a real-world cohort of 1403 participants from the Canadian Obstructive Lung Disease study who underwent spirometry to detect COPD; linked health administrative data were queried to identify pre-existing physician diagnoses of COPD. Undiagnosed COPD was detected in 13.7% of the participants, 5.1% were overdiagnosed and 3.7% had been correctly diagnosed. Compared with participants without COPD, those with overdiagnosed COPD had significantly more hospitalisations, ED visits and ambulatory care visits, and those with moderate-to-severe undiagnosed COPD also had more hospitalisations.

Comment: This article should be read in conjunction with a report from our Australian colleagues on substantial variation in spirometry interpretation practices and the article from our European colleagues that 'Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests'. The chosen publication from Canada makes the point that it matters. Based on the Canadian Obstructive Lung Disease study, the authors found that overall a misdiagnosis of COPD occurred five times more often than correctly diagnosed COPD. **Bottom line: patients without a correct diagnosis of COPD (underdiagnosed) and patients with wrongly diagnosed COPD (overdiagnosed) have increased health services needs.**

Reference: Chest 2018;153:1336–46
Abstract

KINDLY SUPPORTED BY
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Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

Seasonal temperature variability and emergency hospital admissions for respiratory diseases

Authors: Sun S et al.

Summary: The relationship between intraseasonal temperature variability and respiratory disease hospitalisations in the elderly was explored in a prospective, Chinese population-based cohort of 66,820 individuals aged ≥65 years. There were 12,689 cases of incident respiratory diseases over 10–13 years of follow-up, of which 6672 were pneumonia and 3075 were COPD. Each 1°C increase in wintertime temperature variability was associated with an increase in the risk of respiratory diseases overall (hazard ratio 1.20 [95% CI 1.08, 1.32]), and for pneumonia and COPD specifically (1.15 [1.01, 1.31] and 1.41 [1.15, 1.71], respectively); no significant associations were detected for summertime temperature variability.

Comment: It probably doesn't need a scientific study to document that winter is associated with an increased number of respiratory infections, exacerbations of COPD and pneumonia. These researchers from Hong Kong contribute a truly prospective study on more than 60,000 Chinese above the age of 65 years. They match data from weather monitoring stations and hospital admissions over a 10-year period. In their discussion, the authors argue why this study is relevant for climate zones with even higher temperature variation and why the effect is likely to worsen with global warming. **Bottom line: the authors found an association between temperature variability and the increased incidence of respiratory disease.**

Reference: Thorax 2018;73:951–8
Abstract

A randomized trial of e-cigarettes versus nicotine-replacement therapy

Authors: Hajek P et al.

Summary: This trial randomised 886 adults attending UK stop-smoking services to either nicotine-replacement products of their choice for ≤3 months or an e-cigarette starter pack with a recommendation to purchase further e-liquids of their choice when needed. All individuals received weekly behavioural support for ≥4 weeks. The 1-year abstinence rate (primary endpoint) was greater in the e-cigarette group than in the nicotine-replacement group (18.0% vs. 9.9% [p<0.001]). Among participants abstinent at 1 year, a greater proportion from the e-cigarette group were still using their assigned product at 52 weeks compared with those assigned to nicotine replacement therapy (80% vs. 9%). Throat or mouth irritation was reported more frequently in the e-cigarette group (65.3% vs. 51.2%) and nausea was reported more frequently in the nicotine-replacement group (37.9% vs. 31.3%). The e-cigarette group reported greater decreases in cough and phlegm production over 1 year than the nicotine-replacement group.

Comment: It would have been easy to fill this whole issue of Respiratory Research Review with articles on e-cigarettes. This article is accompanied by two editorials, one summarising that 'E-cigarettes assist with smoking cessation', the other highlighting 'The dangerous flavors of e-cigarettes'. This is a multicentre, pragmatic, randomised trial of e-cigarettes as compared with nicotine-replacement therapy in addition to behavioural support. Smoking cessation at 1 year was validated by measurement of exhaled carbon monoxide levels. **Bottom line: after 1 year, 18% in the e-cigarette group were smoke-free and about 10% in the nicotine replacement group. After 1 year, 80% were still using e-cigarettes and only 9% using nicotine replacement.**

Reference: N Engl J Med 2019;380:629–37
Abstract

Early-onset emphysema in a large French-Canadian family

Authors: Bossé Y et al.

Summary: These authors sought to identify the genetic cause of early-onset emphysema in 63 members covering five generations of a French-Canadian family without A1AT (α-1 antitrypsin) deficiency; 55 of the family members had available DNA for analysis. Whole-exome sequencing was performed in a convenience sample of 14 individuals, including nine with unambiguous expression of the typical form of emphysema observed in the family. They identified a rare inherited variant in the *PTPN6* gene that caused the early onset of emphysema in this family, which is believed to be the second form of hereditary emphysema since A1AT deficiency was discovered. The authors comment that their findings represent a breakthrough in the understanding of emphysema genetics and pathogenesis.

Comment: In addition to environmental factors like smoking, indoor unflued cooking and others, researchers are also looking for genetic predispositions. The genetic mutation causing A1AT deficiency was described more than 50 years ago. This is a beautiful paper studying a single family, utilising whole-exome sequencing and identifying a new genetic mutation of a key regulator of the immune process. The newly described mutation is rare, i.e. less than 2:100,000 compared with 25:100,000 for A1AT deficiency. **Bottom line: this finding of a failure to suppress lung immunity supports the concept of an AT autoimmune process in the development of emphysema.**

Reference: Lancet Respir Med 2019;7:427–36
Abstract

Surgical and endoscopic interventions that reduce lung volume for emphysema

Authors: van Geffen WH et al.

Summary: This systematic review and meta-analysis included 20 RCTs (n=2794) investigating lung volume reduction for emphysema. Compared with sham procedures or standard of care, lung volume reduction from any intervention (surgical, endobronchial valve, endobronchial coil or sclerosing agents) was associated with a reduction in mean residual volume of 0.58L, an increase in FEV_1 of 15.87%, an improvement in 6MWD of 43.28m and a reduction in SGRQ score of 9.39 points. Lung volume reduction interventions were associated with an increased risk of a severe adverse event (odds ratio 6.21 [95% CI 4.02, 9.58]). A regression analysis revealed improvements relative to the degree of volume reduction: FEV_1 (r^2=0.86 [p<0.0001]), 6MWD (r^2=0.77 [p<0.0001]) and SGRQ score (r^2=0.70 [p<0.0001]). The risk of bias was high for most studies due to lack of blinding, and heterogeneity was high for some outcomes when pooled across all interventions.

Comment: Medical lung volume reduction is using endobronchial valves, endobronchial coils or a sclerosing agent to reduce hyperinflation, the work of breathing and mechanical constraints on lung expansion to improve QOL, 6MWD and lung function as measured by the FEV_1. In this systematic review and meta-analysis, the authors extracted individual data from RCTs and compared the therapeutic effects and adverse events between routine care, endoscopic interventions and surgical treatment. **Bottom line: the mechanical interventions that reduced residual volume lead to improved lung function, QOL and exercise capacity.**

Reference: Lancet Respir Med 2019;7:313–24
Abstract

Triple therapy versus single and dual long-acting bronchodilator therapy in COPD

Authors: Cazzola M et al.

Summary: These researchers conducted a meta-analysis to compare triple ICS, LABA and LAMA therapy with LABA/LAMA combinations or single long-acting bronchodilators in COPD. Compared with LABA/LAMA combination therapy, triple therapy was associated with a reduced exacerbation risk (relative risk 0.70 [95% CI 0.53, 0.94]), particularly among patients with blood eosinophil counts ≥300 cells/μL (0.57 [0.48, 0.68]); triple therapy also improved trough FEV_1 (mean difference 37.94mL). The NNT with triple therapy to prevent one exacerbation per year was ~38 when compared with dual LAMA/LABA therapy, but fell to ~21 when compared with single long-acting bronchodilator therapy. The person-based NNT per year for triple therapy versus LABA/LAMA therapy was significantly lower in patients with eosinophil counts ≥300 cells/μL than in those with lower counts (8.58 vs. 46.28). There was no significant difference between triple therapy and the comparators for risk of pneumonia, with an NNH of ~195.

Comment: International guidelines suggest triple therapy (ICS/LABA/LAMA) to be prescribed for patients with the most severe COPD, about 10% of the cohort. However, national (Respiratory Research Review, issue 149) and international evidence suggests the majority of patients receiving triple therapy have mild-to-moderate disease. These researchers from Rome extracted data from about 17,000 patients with COPD who participated in RCTs. They acknowledged the effect of the large IMPACT study (Respiratory Research Review, issue 149), which may have included a significant number of patients with asthma. **Bottom line: the NNT with triple therapy versus LABA/LAMA therapy was 38. It was lower in patients with blood eosinophilia.**

Reference: Eur Respir J 2018;52:1801586
Abstract

CLICK HERE to read previous issues of Respiratory Research Review

12-month randomised controlled trial of ginseng extract for moderate COPD

Authors: Shergis JL et al.

Summary: Study participants aged ≥40 years with moderate airflow limitation according to GOLD (n=168) were randomised 1:1 to receive 24 weeks of ginseng capsules 100mg twice daily or placebo for 24 weeks and were followed for a further 24 weeks in this trial. No significant difference was detected between the ginseng and placebo groups for SGRQ, COPD Assessment Test or the Short Form Health Survey score, lung function, exacerbation rate or relief medication use; overall improvements were recorded for both groups. Ginseng was well tolerated.

Comment: Bronchodilators and ICSs are of limited benefit in COPD and have adverse effects. It has been estimated that up to 40% of patients use herbal remedies to treat COPD. Ginseng is promising because of its anti-inflammatory effects, and inhibition of proinflammatory mediators. This co-operative study between Melbourne and Guangzhou compares ginseng versus placebo in patients with mild to moderately severe COPD for 52 weeks. The authors were comprehensive in their description of the Chinese origin and Swiss manufacturing of the ginseng. **Bottom line: QOL and reliever medication use improved in both groups. No difference was seen in lung function, adverse events or exacerbations.**

Reference: Thorax 2019;74:539–45
Abstract

Inpatient palliative care of people dying in New South Wales hospitals or soon after discharge

Authors: Stubbs JM et al.

Summary: Hospital use during the final year of life, timing of palliative care and variations by age and disease for patients receiving inpatient palliative care were reported for a retrospective cohort of 150,770 Australians who died at age ≥50 years either while still in hospital or within 30 days of discharge. Around one-third of decedents (34.4%) received palliative care a median of 10 days prior to death, and this was more likely among those with cancer versus those with other chronic conditions (64.7% vs. 13.3%) and those who were younger (46.3% vs. 25.0%). Palliated decedents had on average three ED presentations and four hospital admissions during their final year of life, including one involving surgery and one with palliative intent. Of the 30.1 hospital days, 8.7 days included palliative care. Decedents who had more days of inpatient palliation and shorter times between first palliative admission and death were of older age and had noncancer diagnoses. Decedents who died outside of a hospital setting had started palliative care 18 days earlier than those who died while in hospital.

Comment: International guidelines suggest that palliative care should be available to all patients with life-limiting conditions. These Sydney authors reviewed all 150,000 deaths in New South Wales over 5 years. The median age was 81 years, and 94% died in hospital or within 30 days of discharge. Overall, about one third received palliative care; these patients were more likely to have cancer or to be younger. Many patients only received palliative care in their last 10 days of life, limiting its effectiveness. **Bottom line: older patients and patients with chronic conditions were less likely to receive palliative care.**

Reference: Intern Med J 2019;49:232–9
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

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Cluster-randomised trial of a nurse-led advance care planning session in patients with COPD and their loved ones

Authors: Houben CHM et al.

Summary: Patients with advanced COPD were randomised by cluster to an intervention of 1.5 hours of structured nurse-led advance care planning sessions (n=89) or a control group (n=76). Compared with the control group, participants assigned to the intervention had a significantly better improvement in the quality of patient-physician end-of-life care communication ($p<0.001$) and a greater likelihood of a discussion regarding advance care planning with their physicians within 6 months ($p=0.003$), and their loved ones had significantly reduced symptoms of anxiety at follow-up ($p=0.02$). There was no significant between-group difference for symptoms of anxiety or depression among participants, for depressive symptoms among their loved ones ($p>0.05$), or for the quality of death or dying ($p=0.17$).

Comment: Despite the high mortality, advanced care planning is uncommon in patients with COPD. The unpredictable trajectory, lack of time and concerns that advanced care planning sessions may cause distress are barriers. This is a courageous trial from the Netherlands to explore the impact a 90-minute nurse-led advanced care planning session had on the quality of end-of-life care communication, as well as anxiety and depression in patients and their loved ones. **Bottom line: a one-off session with a nurse specialist improved communication about end-of-life care, did not cause depression or anxiety in the patients, and reduced anxiety in the loved ones at 6-month follow-up.**

Reference: Thorax 2019;74:328–36
Abstract