Respiratory RESEARCH REVIEW™

Making Education Easy

Issue 180 – 2020

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Abbreviations used in this issue
COPD = chronic obstructive pulmonary disease
DALY = disability-adjusted life-year
D_{LCO} = diffusing capacity of the lung for carbon monoxide
FEV = forced expiratory volume
HR = hazard ratio
ICS = inhaled corticosteroid
LABA = long-acting β-agonist
LAMA = long-acting muscarinic antagonist

Welcome to the last issue of Respiratory Research Review of the year 2020.

This has certainly been a memorable year and history will provide the final verdict on its impact. COVID-19 has changed our health landscape and has brought increased suffering and death across the world. It has also assisted us to reconsider the importance of public health, caused a pause in the annual influenza season, led to an appreciation of science, and in some settings has even been associated with increased funding. How will we view 2020 in the future? What are your predictions?

The respiratory focus of this final research review is COPD, and the number of high-impact publications makes it difficult to select ten representative articles. One hot topic is certainly the role of ICSs in COPD. In asthma care, ICSs have moved centre stage, with local and international guidelines recommending that all patients with asthma should be treated with ICSs. The new guidelines see no role for therapy with short-acting β-agonists only. The role of ICSs in COPD is less clear; the evidence is best for patients with >2 exacerbations per year and patients with blood eosinophilia. Overall, ICSs in COPD are probably overprescribed and increase the risk of pneumonia, mycobacterial diseases, osteoporosis and oropharyngeal candidiasis. 'Withdrawal of inhaled corticosteroids in COPD: a European Respiratory Society guideline' provides a clinical helpful flowchart and three recommendations:

1) Conditional recommendation to withdraw ICSs in patients with COPD without a history of frequent exacerbations.
2) Strong recommendation not to withdraw ICSs in patients with a blood eosinophil count of ≥300 eosinophils/μl.
3) Strong recommendation to treat with one or two long-acting bronchodilators if ICSs are withdrawn.

Before we get into the main body of the review, we are going to reflect on editorials related to the IMPACT study. Peter Calverley writes one of the editorials, which is clinically astute, and he cites St. Thomas Aquinas and Karl Popper. The title of his editorial is: 'Angels dancing on the tip of a needle: interpreting clinical trials in chronic obstructive pulmonary disease'.

Paul Enright and Carlos Vaz Fragoso are less poetic, however, they are also evidence based, where they remind us in their commentary that epidemiological definitions don't easily translate into clinical practice. They review some of the investigations a diagnosis of COPD is based on. For example, in a UK study of nearly 50,000 patients with COPD, only about 20% ever had spirometry, and of these about a quarter did not have airways disease. 'GPs should not try to detect mild COPD' is fraught with difficulty, and we have no proven treatment to slow the progression of COPD besides smoking cessation.

In this final issue of the year, three themes may help assist us in planning for the next year in our personal and professional development.

1) The high-quality publication on the 'Association of daily step count and step intensity with mortality among US adults', which showed that a greater number of steps per day were associated with a lower risk of all-cause mortality. This article is supported by the BMJ study based on half a million adults on the 'Recommended physical activity and all cause and cause specific mortality in US adults'. This is a prospective cohort study, which confirms that people who adhere to the US activity guidelines have a greatly reduced risk of all-cause and cause-specific mortality.
2) The debate/review on 'identifying recommendations for stopping or scaling back unnecessary routine services in primary care'.
3) And finally, a paper that I found via a Nature Briefing, which has led to a wide debate amongst friends/colleagues: 'The mundanity of excellence: an ethnographic report on stratification and Olympic swimmers'.

Thank you for your support and interest during this year. We hope you enjoy this selection and have the opportunity of a break over the summer.

Kind regards,

Professor Lutz Beckert
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Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017

Authors: GBD Chronic Respiratory Disease Collaborators

Summary: This systematic analysis of the GDB (Global Burden of Disease) study estimated the prevalence, morbidity and mortality attributable to chronic respiratory diseases between 1990 and 2017. There were an estimated 544.9 million people worldwide with chronic respiratory diseases in 2017, a 39.8% increase from 1990. The highest prevalences were seen in high-income regions, and the lowest were in sub-Saharan Africa and south Asia. In 2017, chronic respiratory diseases were the third leading cause of death after cardiovascular diseases and neoplasms. There were 3,914,196 deaths from chronic respiratory diseases in 2017, an 18% increase since 1990, with a 13.3% increase in total DALYs; however, declines of 14.3%, 42.6% and 38.2% were evident in age-standardised prevalence, death rate and DALY rate, respectively, after accounting for aging and population growth. Interstitial lung disease and pulmonary sarcoidosis were associated with higher mortality than pneumoconiosis. The leading risk factor for chronic respiratory disease-related disability for men worldwide was smoking, while for women from southeast Asia, east Asia, Oceania, the Middle East and north Africa, the main risk factor was ambient particulate matter; in women from south Asia and sub-Saharan Africa, it was household air pollution from solid fuels. COPD was responsible for most chronic respiratory disease-attributable deaths and DALYs.

Comment: The Chronic Respiratory Disease Collaboration has now confirmed that chronic respiratory illness is the third leading cause of death following cardiovascular illness and neoplasms. It is sobering to think that we have had 62 million coronavirus infections and 1.4 million deaths (43 million have recovered). In 2017, 545 million people lived with chronic respiratory illness and 3.9 million died from it. Premature death from chronic respiratory illness is higher in poorly resourced health systems. **Bottom line: the main cause for chronic respiratory disease-related disability for women was cooking with solid fuels, and for men it was smoking; both are preventable.**

Reference: Lancet Respir Med 2020;8:585–96
Abstract

Lung function trajectories leading to chronic obstructive pulmonary disease as predictors of exacerbations and mortality

Authors: Marott JL et al.

Summary: Long-term COPD exacerbation and mortality risks were compared between young adults from the Copenhagen City Heart Study (n=1170) who developed COPD through a normal maximally attained FEV_1 trajectory (n=79) versus a low maximally attained FEV_1 trajectory (n=65). Severe COPD exacerbations were recorded between 2001 and 2018 for 139 participants, and there were 215 deaths (55 due to nonmalignant respiratory disease). No significant difference was detected between the two FEV_1 trajectories and severe COPD exacerbation risk, but participants from the normal maximally attained FEV_1 group were at increased risk of death due to nonmalignant respiratory disease and any cause than those from the low maximally attained FEV_1 group (respective adjusted HRs 6.20 [95% CI 2.09, 18.37] and 1.93 [1.14, 3.26]).

Comment: Of all patients diagnosed with COPD, about half start with full lung function and suffer an accelerated decline, mainly because of smoking. Roughly, another half of the COPD population have equally low FEV_1 measurements because their lungs have never reached their full potential, chiefly because of prematurity or childhood illnesses (Respiratory Research Review issue 119). These authors confirmed these findings in about 15,000 participants of the Copenhagen City Heart Study, followed for 17 years. **Bottom line: patients who had a low lung function because of smoking had a faster deterioration of lung function and increased mortality.**

Reference: Am J Respir Crit Care Med 2020;202:210–8
Abstract

For more information, please go to www.medsafe.govt.nz

Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries

Authors: Lindenauer PK et al.

Summary: This retrospective cohort study used US Medicare data from 197,376 patients hospitalised with COPD to examine the relationship between initiation of pulmonary rehabilitation within 90 days of hospital discharge (n=2721) and 1-year survival. The 1-year mortality rate was 7.3% for patients initiating pulmonary rehabilitation within 90 days, and it was 19.6% for those initiating pulmonary rehabilitation after 90 days or not at all. Initiation within 90 days was associated with a lower risk of death over 1 year (HR 0.63 [95% CI 0.57, 0.69]). Pulmonary rehabilitation was associated with lower mortality from ≥30 days (HR 0.74 [95% CI 0.67, 0.82]) to 61–90 days after discharge (0.40 [0.30, 0.54]); every three rehabilitation sessions were associated with a reduction in risk of death (0.91 [0.85, 0.98]).

Comment: Pulmonary rehabilitation is one of the most effective treatments available to improve quality of life, increase walking distance and reduce readmissions. It is sobering to see that in this meta-analysis, the authors estimated that 15 million people live with COPD in the US, with 1.5 million visits to emergency departments and about 700,000 hospital admissions, with a 1-year mortality of 26%. This meta-analysis captures about 200,000 admissions, and a total of 2721 (1.5%) participated in a pulmonary rehabilitation programme within 90 days of admission. This suggests a shortfall of pulmonary rehabilitation capacity. **Bottom line: patients who participated in pulmonary rehabilitation within 3 months had significantly reduced mortality at 1 year.**

Reference: JAMA 2020;323:1813–23
Abstract

A geographic analysis of racial disparities in use of pulmonary rehabilitation after hospitalization for COPD exacerbation

Authors: Spitzer KA et al.

Summary: These researchers explored if pulmonary rehabilitation programme density could be the cause of observed regional variations and racial disparities seen for receipt of such programmes among 223,832 US Medicare beneficiaries hospitalised for COPD during 2012. There was a median of 0.06 pulmonary rehabilitation programmes per 1000 Medicare beneficiaries, with risk-standardised rates ranging from 0.53% to 6.67%. Significant positive associations were seen between the density of pulmonary rehabilitation programmes and pulmonary rehabilitation rates overall and among non-Hispanic white beneficiaries, but not black beneficiaries, with a higher median rate among non-Hispanic white versus black beneficiaries (2.08% vs. 1.19%).

Comment: Pulmonary rehabilitation is the most cost-effective intervention to improve the quality of life of patients with COPD. In the US, fewer than 2% of patients participate in pulmonary rehabilitation despite spending almost US$50 billion on COPD care. Participation in pulmonary rehabilitation depends on the availability, frequency and race, with black Americans participating less than non-black. The authors reflect on possible reasons and for us NZ readers, we should read Peter Crampton's editorial in N Z Med J, titled 'Oh my'. **Bottom line: pulmonary rehabilitation is effective and needs to be more available, and we need to be mindful of barriers.**

Reference: Chest 2020;157:1130–7
Abstract

Each month we highlight a particularly excellent paper with our butterfly symbol.

Re-evaluation of the UPLIFT clinical trial using age-appropriate spirometric criteria

Authors: Vaz Fragoso CA et al.

Summary: These researchers sought to determine if age-appropriate criteria for airflow obstruction from the GLI (Global Lung Function Initiative) would modify the spirometric classification of the 5898 participants from the UPLIFT cohort, whose mean age was 65 years. For the cohort, GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria for airflow-obstruction staged 46.6% as moderate and 53.5% as severe, whereas according to the GLI-based criteria (n=5750), 13.5% were staged as moderate and 83.9% as severe. Compared with placebo, tiotropium did not have a significant overall impact on mortality in GLI- and GOLD-based airflow obstruction (respective adjusted HRs 0.91 [95% CI 0.80, 1.04] and 0.91 [0.79, 1.03]); however, there was a statistically significant effect for moderate but not severe airflow obstruction according to GLI criteria (0.53 [0.34, 0.81] and 0.99 [0.86, 1.13], respectively; p=0.007 for interaction).

Comment: This article is an exercise on what happens when one applies scientifically based lung function criteria, like the GLI, rather than criteria with arbitrarily chosen cut-points, like GOLD. The authors re-evaluated spirometry data of almost 6000 participants of the UPLIFT study, reclassified them using GLI, and estimated the impact on survival. For a review of the clinical use of tiotropium, use this link. See this editorial for a discussion about the 'cut to the chase: cut-points for use in interpretation of pulmonary lung function tests'. **Bottom line: using a statistically based approach diagnoses COPD more accurately and identifies subgroups with improved mortality on treatment with tiotropium.**

Reference: Chest 2020;158:539–49
Abstract

Diffusing capacity is an independent predictor of outcomes in pulmonary hypertension associated with COPD

Authors: Balasubramanian A et al.

Summary: The value of D_{LCO} for predicting mortality was evaluated in a retrospective cohort of 71 registrants with COPD with pulmonary hypertension. The respective unadjusted transplant-free 1-, 3- and 5-year survival rates were 87%, 60% and 51%. Associations were seen between survival and reduced D_{LCO} values across the range of pulmonary artery pressures and pulmonary vascular resistances. Severe D_{LCO} impairment was associated with significantly poorer survival, with each percent predicted decrease in D_{LCO} associated with a significant increase in the risk of death (HR 1.04 [95% CI 1.01, 1.07]).

Comment: The last article used evidence-based spirometric criteria to tailor treatment; this article is using D_{LCO} to predict survival in COPD patients. The authors identified a cohort of 71 patients with COPD-related pulmonary hypertension. Patients with a D_{LCO} ≤50% predicted had higher pulmonary resistance, a reduced performance status, and a reduced 6-minute walk distance, despite a mean FEV_1 of 52%. Before reaching for pulmonary vasodilators, we need to pause, as these increased pulmonary artery pressures may be a compensatory mechanism (Respiratory Research Review issue 177 and issue 178). **Bottom line: a reduced D_{LCO} is associated with increased mortality in COPD.**

Reference: Chest 2020;158:722–34
Abstract

Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD

Authors: Rabe KF et al. for the ETHOS Investigators

Summary: This 52-week, randomised phase 3 trial tested triple fixed-dose regimens of a LAMA (glycopyrrolate 18µg), a LABA (formoterol 9.6µg) and two doses of an ICS (budesonide 320µg or 160µg) versus one of two dual therapies (glycopyrrolate 18µg plus formoterol 9.6µg or budesonide 320µg plus formoterol 9.6µg) in 8509 patients with COPD. The annual moderate or severe exacerbation rates were 1.08 in budesonide 320µg recipients (n=2137), 1.07 in budesonide 160µg recipients (n=2121), 1.42 in glycopyrrolate-formoterol recipients (n=2120) and 1.24 in budesonide-formoterol recipients (n=2131); budesonide 320µg triple therapy was better than either glycopyrrolate-formoterol (RR 0.76 [95% CI 0.69, 0.83]) or budesonide-formoterol (0.87 [0.79, 0.95]), as was budesonide 160µg triple therapy versus glycopyrrolate-formoterol (0.75 [0.69, 0.83]) or budesonide-formoterol (0.86 [0.79, 0.95]). Adverse event rates were similar across treatment groups and the incidence of confirmed pneumonia was 3.5–4.5% with ICSs versus 2.3% with glycopyrrolate-formoterol.

Comment: Patients with moderate-to-severe, severe or very severe COPD were randomised to receive dual or triple therapy with the aim to reduce exacerbations. Although the authors appropriately selected patients with severe disease, about 31% had reversibility and 15% eosinophilia. Patients on triple therapy had 1.1 exacerbations, and patients on LAMA/LABA therapy had 1.4 exacerbations per year. Patients in the cohort that received ICSs had an increased risk of pneumonia as previously observed, whereas the LABA/LAMA group had the lowest risk of pneumonia. **Bottom line: in selected groups, triple therapy with ICS/LAMA/LABA reduced COPD exacerbations.**

Reference: N Engl J Med 2020;383:35–48
Abstract

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Azithromycin during acute chronic obstructive pulmonary disease exacerbations requiring hospitalization (BACE)

Authors: Vermeersch K et al., on behalf of the BACE Trial Investigators

Summary: Patients hospitalised for an acute COPD exacerbation with ≥1 exacerbation in the prior year were randomised within 48 hours of admission to receive azithromycin 500 mg/day for 3 days followed by 250mg every second day for 3 months (n=147) or placebo (n=154) added to standard treatment (systemic corticosteroids and antibiotics). At 3 months, the respective treatment failure rates (primary endpoint) in the azithromycin and placebo arms were 49% and 60% (HR 0.73 [95% CI 0.53, 1.01]), the treatment intensification rates were 47% and 60% (p=0.0272), the rates of hospital care step-up were 13% and 28% (p=0.0024) and the mortality rates were 2% versus 4% (p=0.5075), with clinical benefits lost at 6 months.

Comment: This Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalisation (BACE) was an investigator-initiated randomised controlled trial, which is technically negative, probably because the researchers ran out of time and money. Pragmatically, patients were randomised to receive 3 months of azithromycin every second day or placebo. Three patients had QT-interval prolongation and no loss of hearing was identified. Azithromycin treatment improved survival and reduced treatment failure by 18%; however, both endpoints just missed the significance cutoff. **Bottom line: low-dose azithromycin may effectively and safely reduce exacerbations of COPD.**

Reference: Am J Respir Crit Care Med 2019; 200:857–68
Abstract

Effect of olfactory stimulation by L-menthol on laboratory-induced dyspnea in COPD

Authors: Kanezaki M et al.

Summary: The effects of olfactory stimulation by an L-menthol patch on the neural respiratory drive and multidimensional aspects of induced dyspnoea were investigated in 28 patients with COPD and 14 controls in this randomised, placebo-controlled (strawberry-scented patch) and sham-controlled (breathing through a facemask only) crossover study. Compared with sham and placebo, L-menthol was not associated with any change in breathing pattern/timing or neural respiratory drive during inspiratory resistive loading. During inspiratory resistive loaded breathing, the participants with COPD experienced significant alleviation of physical and mental breathing effort, air hunger, breathing discomfort, anxiety and fear with L-menthol, whereas in control participants, there were reductions in air hunger, mental breathing effort and unpleasantness with L-menthol, with no significant improvement on affective dimension of dyspnoea.

Comment: Have you ever had a patient explain to you that an L-menthol inhaler is more effective than their other inhalers? Were you puzzled? L-menthol does not increase the airflow, reduce the respiratory rate or the work of breathing when measured formally. L-menthol stimulates the melastatin 8 receptor in the trigeminal and vagal nerves evoking a sensation of cool/cold temperature. The accompanying editorial summarises: 'Breathlessness isn't cool, but its treatment can be'. **Bottom line: L-menthol can lead to a sensation of coolness and increased airflow, reduce air hunger and palliate breathlessness.**

Reference: Chest 2020;157:1455–65
Abstract

Association between inhaled corticosteroids and tracheobronchomalacia

Authors: Shah V et al.

Summary: This was a retrospective analysis of patients with asthma (n=310) or COPD (n=153), with and without tracheobronchomalacia. The likelihood of tracheobronchomalacia was significantly increased in patients receiving high-dose steroids (odds ratio 3.5 [95% CI 1.4, 8.5]) as well as those receiving LAMAs and those with gastroesophageal reflux disease; age and type of pulmonary disease were also significantly associated with tracheobronchomalacia. Among ICS recipients, high- versus low-dose ICS use significantly increased the likelihood of tracheobronchomalacia (odds ratio 2.9 [95% CI 1.2, 7.1]); type of ICS and number of months of ICS therapy were also significantly associated with tracheobronchomalacia.

Comment: In the introduction, we reflected on the ERS guidelines on withdrawing ICSs in COPD; still, about 50% of patients with COPD are on ICSs at a cost of about US$9 billion in the US alone. These authors identified patients with tracheobronchomalacia, mainly via CT scanning, with a more than 50% reduction in the airway lumen on quiet breathing. Tracheobronchomalacia is associated with reflux disease and with ICS use. The authors are careful not to jump to the conclusion of causation, although a mechanism is plausible. **Bottom line: high-dose ICS use is associated with an increased risk of tracheobronchomalacia.**

Reference: Chest 2020;157:1426–34
Abstract

Independent commentary by Professor Lutz Beckert

Professor Lutz Beckert is the Associate Dean Medical Education with 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.

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