Making Education Easy

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Abbreviations used in this issue:

ACQ-5 = Asthma Control Questionnaire-5; **ARDS** = acute respiratory distress syndrome; **COPD** = chronic obstructive pulmonary disease; **ECMO** = extracorporeal membrane oxygenation; **Fe_{NO}** = fractional exhaled nitric oxide; **FEV_1** = forced expiratory volume in 1 second; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **HR** = hazard ratio; **ICS** = inhaled corticosteroid; **IRR** = incidence rate ratio; **PAH** = pulmonary arterial hypertension; **ppb** = parts per billion; **RCT** = randomised controlled trial; **SLE** = systemic lupus erythematosus; **TB** = tuberculosis.

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Welcome to issue 77 of Respiratory Research Review.

One of the papers in this issue discusses findings from a large Chinese epidemiological study that examined associations between solid fuel use for cooking and risks of acute and chronic respiratory diseases among adults. Over 9 years of follow-up, those using solid fuel use for cooking were at greater risk of major respiratory disease hospitalisations and death than those who cooked with clean fuel; risks were lower for those who switched to clean fuels or ventilated cookstoves compared with those who did not switch.

In another paper, data from the Cystic Fibrosis Registry of Ireland suggest that improvements in clinical outcomes and reductions in healthcare resource utilisation continue for up to 36 months after commencing ivacaftor treatment.

I hope you find the papers in this issue useful in your practice and I look forward to your comments and feedback.

Kind Regards,

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Airway obstruction and bronchial reactivity from age 1 month until 13 years in children with asthma: a prospective birth cohort study

Authors: Hallas HW et al.

Summary: This paper discusses data from 367 children enrolled in the at-risk Copenhagen Prospective Studies on Asthma in Childhood 2000 ($COPSAC_{2000}$) birth cohort born to mothers with asthma. The children underwent spirometry and methacholine choline challenge tests from age 1 month, plethysmography and bronchial reversibility from age 3 years, cold dry air hyperventilation from age 4 years, and exercise challenge at age 7 years. Ninety-seven (27%) children developed asthma in their first 13 years of life; 270 (73%) did not. Median age at diagnosis was 2.0 years and the median age at remission was 6.2 years. Compared with children who did not develop asthma, those who did had reduced lung function (*z*-score difference, FEV, −0.31; p<0.001), increased airway resistance (*z*-score difference, specific airway resistance, +0.40; p<0.001), increased bronchial reversibility (difference in ΔFEV_1, +3%; p<0.001), increased reactivity to methacholine (*z*-score difference for provocative dose, −0.40; p<0.001), decreased FEV at cold dry air challenge (ΔFEV_1, −4%; p<0.01) and decreased FEV after exercise (ΔFEV_1, −4%; p=0.02).

Comment: The traditional hypothesis of asthma onset is that airway inflammation develops first and then airway obstruction and remodelling result as a consequence. However, a growing counterproposal is that increased airway obstruction and airway reactivity may in fact precede airway inflammation. This study from a Copenhagen high-risk for asthma childhood cohort assessed the children from 1 month of age with infant lung function and then until 13 years. The study demonstrated that airway obstruction and bronchial hyperreactivity were present before symptoms began, independent of disease duration, and did not improve with symptom remission. This suggests that airway obstruction and bronchial hyperreactivity are stable traits of childhood asthma and do not tend to develop after birth.

Reference: PLoS Med. 2019;16(1):e1002722

Abstract

Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis

Authors: Munshi L et al.

Summary: This systematic review of the literature examined the clinical evidence on the effect of venovenous ECMO on mortality related to ARDS. Five studies (2 RCTs and 3 observational studies) satisfied the inclusion criteria and were included in the review; all involved conventional mechanical ventilation with and without venovenous ECMO in a total of 773 adults with ARDS. The primary outcome of 60-day mortality was assessed in both RCTs and was significantly lower in patients who received venovenous ECMO than in those who did not (34% vs 47%; RR 0.73, 95% CI, 0.58 to 0.92; p=0.008); an assessment of the data using GRADE guidelines demonstrated a moderate level of evidence for this outcome. However, ECMO was associated with a risk of major haemorrhage, which was reported by 3 studies; of the 251 patients in those studies, 48 (19%) had major haemorrhages.

Comment: Venovenous ECMO has increasingly been used to support ARDS since the 2009 influenza pandemic. This systematic review examined two RCTs and three observational studies of 773 patients with ARDS and found that 60-day overall mortality was significantly lower in the ECMO group. It further confirms that ECMO is the supportive treatment of choice in the clinical setting of ARDS.

Reference: Lancet. 2019;7(2):163-72
Abstract

RESEARCH REVIEW
The Australian Perspective Since 2007

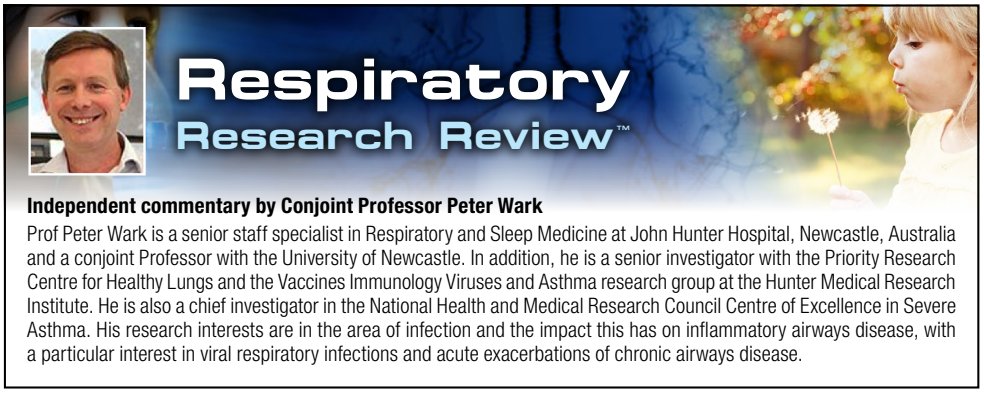
Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma

Authors: Heaney LG et al.

Summary: This UK study recruited 250 individuals with difficult-to-control asthma in routine clinical care; all were receiving standard high-dose ICS and long-acting β_2-agonists. The study researchers sought to determine the feasibility and utility of clinical care via a web-based interface using integrated remote monitoring technology delivering fractional exhaled nitric oxide (Fe_{NO}) suppression testing. Clinical response to treatment was assessed using the ACQ-5, spirometry, and biomarker measurements (Fe_{NO} and peripheral blood eosinophil count). A total of 201 patients completed the test with 130 positive suppression tests. Compared with a negative suppression test, a positive test identified a Fe_{NO}-low population when adherent with ICS/long-acting β_2-agonist (median, 26 ppb vs 43 ppb) with significantly greater FEV_1% (mean, 88.2 vs 74.1; p<0.01). Both groups experienced significant improvements in ACQ-5 scores (positive test: mean difference, –1.2; negative test: mean difference, –0.9).

Comment: Inadequate adherence to asthma preventer therapy remains an important cause of poor asthma control. This group of asthma specialists has previously demonstrated that they can utilise suppression of exhaled nitric oxide with supervised inhaled steroid use to detect non-compliance. This study is an extension of this work to a home monitoring system. The study occurred in the context of a severe asthma clinic, where subjects with poor control despite high-dose ICS were recruited. ICS use and technique was recorded automatically on a device, exhaled nitric oxide was monitored at home and symptoms recorded. Of those with Fe_{NO} >45, 65% had a positive suppression test with effective adherence, improved symptoms and lung function, indicating that nonadherence or poor technique were contributing to poor asthma control. Adherence to regular treatment in asthma remains an important area of concern and needs to be considered in the context of use of biologic agents in severe asthma.

Reference: Am J Respir Crit Care Med. 2019;199(4):454-64
Abstract



Independent commentary by Conjoint Professor Peter Wark

Prof Peter Wark is a senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital, Newcastle, Australia and a conjoint Professor with the University of Newcastle. In addition, he is a senior investigator with the Priority Research Centre for Healthy Lungs and the Vaccines Immunology Viruses and Asthma research group at the Hunter Medical Research Institute. He is also a chief investigator in the National Health and Medical Research Council Centre of Excellence in Severe Asthma. His research interests are in the area of infection and the impact this has on inflammatory airways disease, with a particular interest in viral respiratory infections and acute exacerbations of chronic airways disease.

Activin type II receptor blockade for treatment of muscle depletion in chronic obstructive pulmonary disease. A randomized trial

Authors: Polkey MI et al.

Summary: In this 24-week study, 67 patients with COPD (mean FEV_1, 1.05 L [41.6% predicted]; aged 40–80 years; BMI <20 kg/m^2 or appendicular skeletal muscle mass index ≤7.25 [men] and ≤5.67 [women] kg/m^2), received 2 doses of either bimagrumab 30 mg/kg intravenously (n=33) or placebo (n=34) (at Weeks 0 and 8). Data were analysed from 55 patients who completed the study. Bimagrumab was associated with increases in thigh muscle volume (cm^3) after 4 weeks of treatment and remained increased at the 24-week follow-up, whereas placebo-treated patients experienced no change (Week 4: +5.9% vs 0.0%; p<0.001; Week 24: +5.0% vs –1.3%; p<0.001). Neither study arm experienced significant improvements in 6-minute-walk distance over the 24 weeks of monitoring. Bimagrumab was associated with muscle-related symptoms, diarrhoea and acne, most of which were mild in severity.

Comment: This was an interesting pilot study of bimagrumab, a monoclonal antibody against the activin type II receptors, blocking the negative regulatory activity of myostatin on skeletal muscle. COPD is known to be associated with peripheral skeletal muscle weakness and wasting. The intervention did see a significant improvement in thigh muscle mass when compared to placebo, with what were described as mild side effects. Unfortunately, there was no improvement in 6-minute walk test distance. It is certainly an interesting and novel aspect of treatment. It may be that the 6-minute walk is not a sensitive enough index of change or the intervention could be combined with exercise training to improve functional efficacy. It will be interesting to see if this will be taken forward.

Reference: Am J Respir Crit Care Med. 2019;199(3):313-20
Abstract

Solid fuel use and risks of respiratory diseases. A cohort study of 280,000 Chinese never-smokers

Authors: Chan KH et al.

Summary: This cohort study recruited 277,838 Chinese adult never-smokers with no prior major chronic diseases at baseline and followed them for 9 years in this examination of the associations of solid fuel use and risks of acute and chronic respiratory diseases. During follow-up, there were 19,823 first hospitalisation episodes or deaths from major respiratory diseases; 10,553 due to chronic lower respiratory disease (CLRD), 4,398 due to COPD and 7,324 due to acute lower respiratory infection (ALRI). The vast majority (91%) of the participants reported regular cooking and around half (52%) were using solid fuels. In Cox regression analyses adjusted for potential confounders, compared with clean fuel users, solid fuel users were at much greater risk for major respiratory diseases (aHR 1.36; 95% CI, 1.32 to 1.40); the risk was lessened for those who switched from solid to clean fuels (1.14; 1.10 to 1.17). The risks of respiratory diseases were higher among those who used wood (aHR 1.37; 95% CI, 1.33 to 1.41) than in those using coal (1.22; 1.15 to 1.29) and in those with prolonged use (≥40 years; 1.54; 1.48 to 1.60; <20 years; 1.32; 1.26 to 1.39), but lower among those using ventilated cookstoves than in those using nonventilated cookstoves (1.22; 1.19 to 1.25 vs 1.29; 1.24 to 1.35). For CLRD, COPD and ALRI, the adjusted HRs associated with solid fuel use were 1.47 (95% CI, 1.41 to 1.52), 1.10 (1.03 to 1.18), and 1.16 (1.09 to 1.23), respectively.

Comment: This large Chinese epidemiological study prospectively assessed the risk of hospitalisation for chronic lung disease in over 200,000 non-smokers. They found that solid fuel use, especially wood and coal, were associated with an increased risk of hospital admission, along with prolonged exposure and the use of unventilated cooking devices. An association between indoor biomass pollution exposure and the development of chronic lung disease has been known for some time. However, this is the largest study to test this association as an independent risk. Interestingly, it shows the strength to be time-dependent, but also that it can be reduced by switching to clean fuel sources for cooking. It emphasises this as an important cause of chronic lung disease in the developing world.

Reference: Am J Respir Crit Care Med. 2019;199(3):352-61
Abstract

Longitudinal trends in real-world outcomes after initiation of ivacaftor. A cohort study from the Cystic Fibrosis Registry of Ireland

Authors: Kirwan L et al.

Summary: These researchers analysed clinical outcomes from 80 patients aged 6–56 years with cystic fibrosis (CF) registered with the CF Registry of Ireland; all had ≥36 months of data before and after commencing treatment with ivacaftor. In the 36 months after ivacaftor initiation, FEV_1% predicted improved by 2.26% per annum for patients aged <12 years, did not change in the 12–17-year age group, and declined in adults by 1.74% per annum. BMI in adults increased 0.28 kg/m^2 per annum; BMI *z*-scores did not change significantly in children. At 12 months after commencing ivacaftor treatment, the use of intravenous antibiotic treatment reduced by 46% and oral antibiotic treatment by 49%, whereas there was no significant reduction in hospitalisation.

Comment: This study describes the real-world effectiveness of treatment with ivacaftor in the Irish CF population. The trial confirms the results seen in the international effectiveness studies, but the long-term follow-up of 36 months adds granularity to these results that could not be seen otherwise. It confirms sustained improvement in lung function, BMI and exacerbation reduction, as well as reduced health care utilisation. The value of registries in demonstrating effectiveness outcomes being delivered in real-world settings is increasingly important, especially with the use of expensive therapies such as ivacaftor.

Reference: Ann Am Thorac Soc. 2019;16(2):209-16
Abstract

Generational patterns of asthma incidence among immigrants to Canada over two decades. A population-based cohort study

Authors: Radhakrishnan D et al.

Summary: This population-based, retrospective cohort study obtained provincial health administrative data from the fiscal years 1996–2012 for ~11.7 million residents of Ontario, Canada, 2.2 million of whom were immigrants (arrived in Canada during the study period; >50% were from East and South Asia and the Pacific). The study examined the relative contribution of environmental exposure to asthma risk by comparing asthma rates among recent immigrants compared with long-term residents. Analyses revealed a lower age- and sex-standardised incidence of asthma among immigrants compared with long-term residents (IRR 0.30; 95% CI, 0.30 to 0.30; p<0.001), although asthma incidence was significantly higher among Ontario-born children of immigrants from most world regions compared with children of long-term residents (IRR 1.44; 95% CI, 1.43 to 1.45; p<0.001). The overall incidence of asthma in Ontario decreased between 1996 and 2012 (p<0.001). Immigrants contributed minimally to overall trends in the overall Ontario population asthma incidence.

Comment: This is another large epidemiological survey that confirms the importance of *in utero*/early life exposure and the development of asthma. It reinforces the importance of environmental exposure at this critical time point in leading to disease development in childhood asthma.

Reference: Ann Am Thorac Soc. 2019;16(2):248-57
Abstract

Predicting tuberculosis relapse in patients treated with the standard 6-month regimen: an individual patient data meta-analysis

Authors: Romanowski K et al.

Summary: This systematic review identified 12 RCTs reporting treatment outcomes for patients with TB receiving the WHO standard 6-month regimen. In an analysis of individual patient data from 3 of the studies, of the 1,189 patients with confirmed pulmonary TB who completed therapy, 67 (5.6%) relapsed. In multipredictor analysis, patients who had cavitary disease at baseline and a positive smear at 2 months were at greater risk of relapse (OR 2.3; 95% CI, 1.3 to 4.2) and they had a relapse risk of 10%. In a comparison of area under the curve values for each multipredictor model, there was modest discrimination between low-risk and higher-risk patients, similar to that of the reference model that accounted for age, sex and HIV status.

Comment: This was a useful meta-analysis of what is a very difficult question concerning the rare chance of recurrence of TB when standard 6-month therapy has been completed. There is little literature available and little to inform clinicians. The presence of cavitating disease and persistence of smear positivity at 2 months, probably both reflections of disease aggressiveness or a high infection burden, were associated with relapse risk. This is informative, though further work needs to be done to understand this phenomenon.

Reference: Thorax. 2019;74(3):291-7
Abstract

Long-term prognosis of patients with systemic lupus erythematosus-associated pulmonary arterial hypertension: CSTAR-PAH cohort study

Authors: Qian J et al.

Summary: In this Chinese study, 310 patients with SLE-associated pulmonary arterial hypertension were followed until death (primary endpoint). One-, 3- and 5-year survival rates were 92.1%, 84.8% and 72.9%, respectively; corresponding proportions of patients who achieved their treatment goal were 31.5%, 53.6% and 62.7%, respectively. In multivariate analysis, baseline serositis, 6-minute walking distance >380 m and cardiac index ≥2.5 L/min/m^2 were independent prognostic factors of achieving treatment goal. Patients with baseline serositis were more likely to achieve their treatment goal after intensive immunosuppressive therapy.

Comment: This was a multicentre observational prospective trial of SLE-associated pulmonary hypertension. It demonstrated that when treatment that targeted improved outcomes was successful, it was associated with improved long-term survival. It also demonstrates the better survival seen in the cohort with pulmonary hypertension compared to those with other causes of pulmonary hypertension.

Reference: Eur Respir J. 2019;53(2)
Abstract

RESEARCH REVIEW — The Australian Perspective Since 2007

Impact of smoking status and concomitant medications on the effect of high-dose N-acetylcysteine on chronic obstructive pulmonary disease exacerbations: a post-hoc analysis of the PANTHEON study

Authors: Papi A et al.

Summary: In PANTHEON, patients (current, ex- and never-smokers) with COPD received twice-daily oral N-acetylcysteine 600 mg (n=482) or placebo (n=482) in addition to existing therapy. This post-hoc analysis examined whether smoking status or use of concomitant medications influenced the efficacy of N-acetylcysteine in terms of reducing COPD exacerbations, defined according to healthcare resource utilisation (HCU) criteria. N-acetylcysteine significantly reduced the rate of HCU events by 20% compared with placebo (p=0.0027); the effect was larger in current/ex-smokers (23%; p<0.01). Patients receiving N-acetylcysteine and long-acting inhaled bronchodilator(s) but no ICS had a significant 60% reduction in the rate of exacerbations compared to those receiving placebo, long-acting bronchodilator(s) and ICS (p<0.0001).

Comment: This study is of interest, even though it is a post-hoc analysis of a previous study and questions have been raised as to the applicability of the findings in other populations with COPD, especially in those with lower rates of smoking. The analysis demonstrates that the addition of N-acetylcysteine improved health care utilisation in current/ex-smokers, to a large extent in those treated with long-acting bronchodilator alone, but also though to a lesser extent, those treated also with inhaled steroids. It may raise interest in this as a treatment option to be explored further, though its mode of action remains speculative.

Reference: Respir Med. 2019;147:37-43
Abstract

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