Respiratory Research Review™

Making Education Easy

Issue 80 - 2019

In this issue:

Abbreviations used in this issue:

AHI = apnoea-hypopnoea index;
AUROC = area under the receiver operating characteristic curve;
BMI = body mass index; **COPD** = chronic obstructive pulmonary disease;
CRF = cardiorespiratory fitness; **FENO** = fractional exhaled nitric oxide;
FEV = forced expiratory volume; **FVC** = forced vital capacity;
GI = gastrointestinal; **ILD** = interstitial lung disease;
OSA = obstructive sleep apnoea; **ppb** = parts per billion.

Claim CPD/CME points Click here for more info.

Follow **RESEARCH REVIEW** Australia on Twitter now
@ResearchRevAus
https://twitter.com/ResearchRevAus

Welcome to the eightieth issue of Respiratory Research Review.

This issue begins with research from Melbourne investigating an intervention for hospitalised patients with community-acquired pneumonia that includes advice to prescribe prednisolone, de-escalation from parenteral to oral antibiotics, early mobilisation and screening and treatment for malnutrition. Also from Melbourne comes research suggesting that blood eosinophil counts in hospitalised patients with acute COPD exacerbations could provide potentially useful information to inform management strategies. Other included research from Australia reported FENO values for healthy Aboriginal and/or Torres Strait Islander Australians, looking for differences between these indigenous ethnic groups and investigating the appropriateness of published cutoff values for asthma/atopy. We conclude this issue with a systematic review and meta-analysis examining the efficacy and safety of long-term inhaled antibiotic treatment for adults with bronchiectasis or chronic respiratory tract infections.

We hope you find this update in respiratory research helpful in your everyday practice. Please remember your feedback is greatly appreciated.

Kind Regards,

Dr Janette Tenne

Medical Research Advisor

janette.tenne@researchreview.com.au

Effectiveness of a bundled intervention including adjunctive corticosteroids on outcomes of hospitalized patients with community-acquired pneumonia

Authors: Lloyd M et al., for the Improving Evidence-Based Treatment Gaps and Outcomes in Community-Acquired Pneumonia (IMPROVE-GAP) Implementation Team at Western Health

Summary: This stepped-wedge, cluster-randomised clinical trial enrolled consecutive patients with community-acquired pneumonia from one of two Melbourne hospitals to investigate an intervention of prednisolone acetate 50 mg/day for 7 days with de-escalation from parenteral to oral antibiotics according to standardised criteria; 401 participants received the intervention and 415 comprised a control group. There was no significant difference between the intervention and control groups for the difference in length of stay (unadjusted geometric mean ratio 0.95 [95% CI 0.78–1.16]), or for the secondary outcomes of mortality and readmission; further adjustments for sex and age did not affect the findings. The intervention was associated with a greater proportion of participants experiencing GI bleeding compared with those from the control group (2.2% vs. 0.7%; unadjusted estimated difference, 0.008 [95% CI 0.005–0.010]).

Comment: This was a double blinded study done at two tertiary hospitals in Melbourne. The bundled intervention included treatment with high-dose steroid for 7 days, step down from intravenous to oral antibiotics according to criteria, early mobilisation and malnutrition screening and treatment. The mean age of patients was 76.4 years. The majority of patients in the study had a CORB severity score of 1 or 2. Compliance in completing the recommended 7 days of oral steroids in the intervention arm was only just above 50%. Hyperglycaemia was the most common medication-related complication, and a 2-fold increase in new insulin prescriptions was observed in patients with diabetes in the intervention group. Twelve patients in total developed GI bleeding, of whom nine were in the intervention arm. The only patient requiring transfusion was from the control group. Length of stay was the primary outcome measured and was short in both groups (3 days). Although there was an increase in early mobilisation and nutritional screening in the intervention cohort, overall the interventions showed no improvements in length of stay, mortality or readmission rates.

Reference: JAMA Intern Med 2019;179:1052–60

Abstract

Association between long-term exposure to ambient air pollution and change in quantitatively assessed emphysema and lung function

Authors: Wang M et al.

Summary: These researchers reported longitudinal associations of ambient O_3 (ozone), $PM_{2.5}$ (fine particulate matter), NO_x (oxides of nitrogen) and black carbon exposure with change in emphysema for a cohort of participants from the MESA (Multi-Ethnic Study of Atherosclerosis) Air and Lung studies. Of 7071 participants, 5780 had been assigned to outdoor residential air pollution concentrations at baseline and during follow-up, and had ≥1 follow-up CT scan, and 2772 had ≥1 follow-up spirometric assessment, over a median of 10 years. Median baseline percent emphysema (3%) increased a mean of 0.58 percentage points every 10 years, during which time the mean ambient concentrations of $PM_{2.5}$ and NO_x decreased substantially, whereas O_3 concentrations did not. Baseline ambient O_3, $PM_{2.5}$, NO_x and black carbon concentrations were significantly associated with greater increases in percent emphysema per 10 years (0.13 per 3ppb, 0.11 per 2 μg/m^3, 0.06 per 10ppb and 0.10 per 0.2 μg/m^3, respectively). Significant associations were seen between ambient O_3 and NO_x concentrations during follow-up and greater increases in percent emphysema, and there was also a significant association between baseline and follow-up ambient O_3 concentrations and a greater decline in FEV_1 per 10 years.

Comment: The cohort included participants from the MESA Air and Lung studies. The study showed that higher residential concentration exposure to ambient O_3, $PM_{2.5}$, NO_x and black carbon at baseline was associated with increased percentage emphysema on CT. Long-term average concentrations of O_3 did not decline during the years of observation and showed the strongest association with progression of emphysema and decline in lung function. Patients with existing lung disease had faster progression. During follow-up, NO_x was also associated with emphysema progression but not $PM_{2.5}$. Existing regulations have helped reduce ambient NO_x and $PM_{2.5}$ levels, but have had no impact on O_3. This is a concern as climate change has the potential to increase O_3 exposure and increase the risk for chronic lung disease.

Reference: JAMA 2019;322:546–56
Abstract

Low and high blood eosinophil counts as biomarkers in hospitalized acute exacerbations of COPD

Authors: MacDonald MI et al.

Summary: This Australian study evaluated whether blood eosinophil counts predicted treatment response in 341 patients with acute exacerbations of COPD. The patients were grouped according to blood eosinophil count, ranging from low (<50 cells/μL) to high (>150 cells/μL). Exacerbations were considered to be associated with infection if virus testing was positive or C-reactive protein level was ≥20 mg/L. Low blood eosinophil counts were found to be more strongly associated with infection (91% vs. 51.9% [p=0.001]), longer hospital stays (median 7 vs. 4 days [p<0.001]) and lower 12-month survival (82.4% vs. 90.7% [p=0.028]) than high blood eosinophil counts.

Comment: This was an interesting study that tried to define COPD phenotypes based on eosinophil counts. They had two cohorts of patients and in both the use of inhaled corticosteroids was high (77.8%). Patients prescribed oral corticosteroids were ineligible for the study. In both cohorts, eosinophil counts of <50 cells/uL were significantly associated with infection, higher C-reactive protein level and total white cell counts. There was a significant difference between eosinophil groups in hospital length of stay. Hospital discharge within 5 days was achieved in 89% of the eosinophilic versus 42% in the eosinopenic group. Survival at 12 months after hospital discharge was significantly lower in the low versus high eosinophil group. Eosinopenia may be a biomarker of sepsis and mortality. Using corticosteroids in eosinopenic patients may actually result in worse outcomes. Further research into these areas may guide on best management strategies.

Reference: Chest 2019;156:92–100
Abstract

Fractional exhaled nitric oxide values in indigenous Australians 3 to 16 years of age

Authors: Blake TL et al.

Summary: FENO levels were measured in 1036 indigenous Australians aged 3–16 years classified as healthy (no asthma or atopy history), asthmatic and/or atopic. No differences were seen among indigenous ethnicities for median FENO values or distribution. Among 390 healthy participants aged <12 years, 7.2% met criteria for the inflammatory zone of the ATS (American Thoracic Society), UK NICE (National Institute for Health and Care Excellence) and BTS/SIGN (British Thoracic Society/Scottish Intercollegiate Guidelines Network) guidelines, whereas this figure dropped to 3.8% for the GINA (Global Initiative for Asthma) guidelines. Among 213 healthy participants aged 12–16 years, the proportion meeting NICE and BTS/SIGN guidelines for the inflammatory zone was greater compared with the ATS and GINA guidelines (9.9% vs. 4.7%).

Comment: This is an important study looking at defining normal ranges of FENO in indigenous populations. Asthma is the most common respiratory illness reported in indigenous Australians, but so far there have been no studies looking at FENO levels in healthy indigenous people. A total of 848 participants were included in the study, with 63% of them being aged <12 years, and the majority had no asthma or atopy. For participants <12 years of age, there was little difference in the median FENO values between the three ethnic groups (Aboriginal, Torres Strait Islander, both). When all the data were combined, 7.2% of healthy participants were considered to have inflammation based on ATS, NICE, BTS and SIGN, which use 35ppb as the cutoff. Only 3.8% had FENO values in the inflammatory zone when using the GINA guidelines (cutoff value >50ppb). Findings were similar in those aged 12–16 years. Based on this study, the GINA recommended cutoff value of 50ppb appears to be the most appropriate for identifying healthy individuals in indigenous children aged 3–16 years. Further research is required to confirm a clinically meaningful cutoff value in this population.

Reference: Chest 2019;156:239–46
Abstract

How OSA evolves from childhood to young adulthood

Authors: Chan KC et al.

Summary: The natural history of OSA (obstructive sleep apnoea) over 10 years from childhood was assessed for a prospective community-based cohort of 243 patients in this research; factors associated with spontaneous remission and persistent and incident OSA into late adolescence/early adulthood were reported. Associations between baseline and follow-up log-transformed obstructive AHI (apnoea-hypopnea index) differed according to age, with a significant positive association seen only among participants aged ≥10 years at baseline. The overall polysomnographic remission rate was 30%, and the proportion with <5 obstructive AHI events per hour at follow-up was 69%. Female sex was associated with complete OSA remission. Adolescent/adult OSA with an obstructive AHI ≥5 events per hour at follow-up occurred at an incidence of 22%. Factors associated with incident OSA were male sex and greater BMI.

Comment: This was a prospective longitudinal study. The mean follow-up period was 10.4 years. At baseline, 40%, 20%, 31% and 9% were normal control subjects, primary snorers and individuals with mild OSA and moderate-to-severe OSA, respectively. Most who were diagnosed with OSA refused treatment. Of those who accepted treatment, 20% had surgery and 13.5% intranasal corticosteroids. Thirty percent of those who had OSA at baseline had complete remission at follow-up. Female sex was associated with complete remission. The incidence of OSA in the study was 22%. Male sex and higher baseline BMI were risk factors. The study showed that OSA diagnosed in late childhood/early adolescence and more severe disease had a higher tendency to persist at follow-up.

Reference: Chest 2019;156:120–30
Abstract

Midlife cardiorespiratory fitness and the long-term risk of chronic obstructive pulmonary disease

Authors: Hansen GM et al.

Summary: This Danish study examined the association between good midlife CRF (cardiorespiratory fitness) and the future risk of COPD in 4730 middle-aged men recruited in 1970–1971 and followed for ≤46 years. Categories of low, normal and high midlife CRF were defined according to maximal oxygen uptake on an ergometer test. Compared with participants with low midlife CRF, the estimated risk of incident COPD was 21% lower with normal CRF and 31% lower with high CRF. The risk of death from COPD was 35% lower with normal midlife CRF and 62% lower with high CRF than with low CRF. Analysis of survival data revealed a delay to incident COPD and death due to COPD of 1.3–1.8 years in participants with normal and high CRF compared with those with low CRF.

Comment: The cohort was drawn from The Copenhagen Male Study from 1970–1971. Mean follow-up was 28.3 years. Mean age at time of study inclusion was 48.7 years. 13.2% had a diagnosis of COPD and 4.9% had COPD registered as cause of death. CRF was measured by VO_{2max}. Low CRF was associated with lower levels of self-reported physical activity, higher BMI, higher alcohol consumption, lower socioeconomic status and higher incidences of diabetes mellitus and arterial hypertension. The estimated risk of incident COPD was reduced by 21% in participants with normal CRF and by 31% in participants with high CRF. Similarly, the risk of COPD-related mortality was significantly reduced in normal CRF and high CRF groups. These results are in keeping with previous studies with shorter follow-up, which have shown a positive association between physical activity and lung function. High midlife CRF was observed to delay time to both diagnosis and death in the magnitude of 1.5–2 years in this study.

Reference: Thorax 2019;74:843–8
Abstract

Comparison of early warning scores in patients with COPD exacerbation

Authors: Echevarria C et al.

Summary: These researchers compared NEWS (National Early Warning Score), NEWS2, $NEWS2_{All\ COPD}$ (NEWS2 for all patients with COPD exacerbation) and DECAF scores at admission for predicting mortality among 2645 consecutive inpatients with COPD exacerbations. Compared with NEWS, NEWS2 identified 3.1% of patients as not needing senior clinician review, and also reduced alerts by 12.6%, which increased to 16.1% when scoring for injudicious oxygen use was excluded. Furthermore, reclassified patients had low mortality. $NEWS2_{All\ COPD}$ was associated with a higher AUROC value for prognosis than NEWS (0.72 vs. 0.65 [p<0.001]) and a similar value compared with NEWS2 (0.72 vs. 0.70 [p=0.090]). However, DECAF was associated with the highest AUROC at 0.82, and its risk stratification range (1.2–25.5%) was more clinically useful than that for NEWS2 (3.5–15.4%).

Comment: The DECAF score has been validated to predict risk of inpatient mortality for patients admitted with COPD exacerbation. It includes dyspnoea, eosinopenia, consolidation, acidaemia and atrial fibrillation. The NEWS is used to monitor patients that are admitted to detect signs of deterioration. It includes respiratory rate, pulse, oxygen saturation, supplemental oxygen, systolic blood pressure, level of consciousness and temperature. A score of 0–4 is low risk, 5–6 is moderate and ≥7 is high risk. This study looked at the usefulness of adding confusion and modified oxygen saturation targets to NEWS, i.e. NEWS2 and $NEWS_{ALLCOPD}$. Data have shown that in COPD patients, low oxygen saturation triggers a number of false alerts, but it is well known that over-oxygenation in this group, especially in patients known to have hypercapnia, is associated with worse outcomes. The study showed that $NEWS_{ALLCOPD}$ did reduce the alerts by 12.6% without adversely affecting patient safety. DECAF score was shown to still be the strongest predictor of mortality.

Reference: Thorax 2019;74:941–6
Abstract

Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP)

Authors: Nathan SD et al.

Summary: Patients aged 18–80 years with pulmonary hypertension associated with idiopathic interstitial pneumonia were randomised to receive riociguat 0.5–2.5mg (n=73) or placebo (n=74) three times daily, followed by open-label riociguat, in the phase 2b RISE-IIP study. High serious adverse event and mortality rates along with absence of efficacy signals in the riociguat arm led to early termination of the study. The respective serious adverse event rates in the riociguat and placebo arms were 37% and 23%, and there had been eight deaths in the riociguat arm and three in the placebo arm, as well as nine during the extension phase, including eight individuals from the former placebo group. The most common adverse events in the main study were peripheral oedema (22% and 9% of riociguat and placebo recipients, respectively) and diarrhoea (15% and 9%), and the most common serious adverse events were worsening of ILD (interstitial lung disease; 8% and 7%) and pneumonia (5% and 1%). Furthermore, there was no significant difference between riociguat versus placebo recipients for the primary endpoint of improvement in 6-minute walk distance (least-squares mean difference, 21m [95% CI –9 to 52]).

Comment: Riociguat has been shown to be beneficial in the treatment of pulmonary arterial hypertension (group 1) and inoperable, persistent or recurrent chronic thromboembolic pulmonary hypertension (group 4). It is known that when patients with ILD develop pulmonary hypertension, they have a worse prognosis. To date the treatment options are limited. Endothelin receptor antagonists have had negative results in previous studies and the data on prostanoids have been conflicting. This study set out to evaluate the efficacy of riociguat in treating pulmonary hypertension secondary to ILD. However, the study was stopped at 26 weeks due to an increased number of adverse events without significant improvements in 6-minute walk distance, oxygen saturation or spirometry. The serious adverse events included worsening of ILD and pneumonia. The other common adverse events were peripheral oedema, diarrhoea, dizziness and hypotension. This study shows that this is an area that urgently needs further research.

Reference: Lancet Respir Med 2019;7:780–90
Abstract

Independent commentary by Dr Alpana Marissa Antony, MBBS, MRCP, FRACP. Dr Antony is a Respiratory and Sleep Physician currently working at St. George Hospital, Sydney as a Staff Specialist in General Medicine. Her areas of clinical interest include respiratory infections, interventional pulmonology and respiratory failure.

The association of body mass index, weight gain and central obesity with activity-related breathlessness

Authors: Ekström MP et al.

Summary: The population-based Swedish Cardiopulmonary Bioimage Study explored the relationship between BMI and breathlessness in 13,437 middle-aged individuals; the participants' mean BMI was 26.8 kg/m^2 and their mean BMI increase since age 20 years was 5.0 kg/m^2, and 9.6% reported breathlessness. A strong relationship was seen between obesity and increased breathlessness (odds ratio 3.54 [95% CI 3.03–4.13]) independent of age, sex, smoking status, airflow obstruction, exercise level and comorbidities. The relationship between breathlessness and BMI steepened as FVC decreased. There was a higher prevalence of breathlessness among obese women than obese men (27.4% vs. 12.5% [p<0.001]), which was related to lower FVC. Individuals whose BMI had increased since the age of 20 years had more breathlessness regardless of current BMI and confounders.

Comment: Breathlessness is associated with higher morbidity and this population-based study looked at whether higher BMI or increase in BMI since the age of 20 years was associated with breathlessness. Over 13,000 participants were included with an average age of 57.5 years. The majority were women. Higher BMI and increase in BMI were both shown to be strongly associated with breathlessness. In the study, the majority showed an increase in BMI over time. Forty-eight percent of individuals with normal BMI at age 20 years had become overweight and 19% obese. There appeared to be a gender disparity, with obese women having more breathlessness than obese men. Individuals with lower absolute FVC had a steeper rise in the probability of breathlessness. But when absolute FVC values were taken into account, the changes in breathlessness in relation to BMI were similar for men and women. However, breathlessness is caused by a number of other factors besides changes in lung function.

Reference: Thorax 2019;74:958–64
Abstract

The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis

Authors: Laska IF et al.

Summary: This was a systematic review with meta-analysis of 16 randomised controlled trials (n=2597) investigating inhaled antibiotics for bronchiectasis and chronic respiratory tract infections in adults. Inhaled antibiotic use was associated with: i) a decrease in colony-forming units per gram of sputum of –2.32 log units (p<0.0001); ii) an increase in bacterial eradication (odds ratio 3.36 [95% CI 1.63–6.91]); and iii) a reduction in exacerbation frequency (rate ratio 0.81 [0.67–0.97]), with prolongation of time to first exacerbation (hazard ratio 0.83 [0.69–0.99]), a lower proportion of patients with ≥1 exacerbation (risk ratio 0.85 [0.74–0.97]) and a significant reduction in severe exacerbation frequency (rate ratio 0.43 [0.24–0.78]). Neither Quality of Life Bronchiectasis questionnaire nor St George's Respiratory Questionnaire score improved above the minimal clinically important difference with inhaled antibiotics, and there was no significant relative change in FEV_1. There was also no significant change in the likelihood of treatment-emergent adverse effects or bronchospasm, but bacterial resistance was evident after treatment (risk ratio 1.91 [95% CI 1.46–2.49]).

Comment: Although there are recommendations for the use of inhaled antibiotics in patients with non-cystic fibrosis bronchiectasis if there is a history of more than 3 exacerbations per year, there is no strong evidence supporting these recommendations. In this review study that included over 2500 patients from 16 international randomised controlled trials, they found that most inhaled antibiotics were generally well tolerated without significant adverse events with the exception of aztreonam. Most therapies showed a reduction of bacterial load and a reduction in exacerbation frequency. But this was not related with improvements in symptoms or quality of life. There was an increase in antibiotic resistance, but this was not associated with treatment failure. Studies that used prolonged continuous treatment regimens did not have significant evidence of resistance, and in others the minimum inhibitory concentration did return to baseline for respective antibiotics after inhaled treatment was ceased.

Reference: Lancet Respir Med 2019;7:855–69
Abstract