Respiratory Research Review™

Making Education Easy

Issue 78 - 2019

In this issue:

Abbreviations used in this issue:

6MWD = 6-min walk distance; **ACQ-5** = Asthma Control Questionnaire-5; **AE** = adverse event; **AF** = atrial fibrillation; **AHI** = Apnoea-Hypopnoea Index; **bpm** = beats per minute; **CAP** = community-acquired pneumonia; **COPD** = chronic obstructive pulmonary disease; **CTEPH** = chronic thromboembolic pulmonary hypertension; **DOAC** = direct oral anticoagulants; **HR** = hazard ratio; **IL** = interleukin; **IR** = impedance ratio; **NREM** = non-rapid eye movement; **OR** = odds ratio; **OSA** = obstructive sleep apnoea; **PhA** = phase angle; **PSI** = Pneumonia Severity Index; **RCT** = randomised controlled trial; **REM** = rapid eye movement; **RR** = risk ratio; **TNF** = tumour necrosis factor; **VKA** = vitamin K antagonist; **VTE** = venous thromboembolism.

Claim CPD/CME points Click here for more info.

Follow **RESEARCH REVIEW** Australia on Twitter now

@ResearchRevAus

https://twitter.com/ResearchRevAus

Welcome to issue 78 of Respiratory Research Review.

In one of the papers in this issue, a meta-analysis of the evidence on the efficacy and safety of DOACs and VKAs during extended anticoagulation for a VTE demonstrates a more favourable net clinical benefit for DOACs compared with VKAs.

In another paper, subcutaneous treprostinil was safe and improved exercise among patients with severe nonoperable chronic thromboembolic pulmonary hypertension (CTEPH). They were randomised to continuous high-dose subcutaneous treprostinil (target dose around 30 ng/kg/min at week 12) or low-dose subcutaneous treprostinil (target dose around 3 ng/kg/min at week 12). In both groups, the most common treatment-related AEs were infusion site pain and other infusion site reactions. The study researchers propose that subcutaneous treprostinil may be feasible for patients in WHO functional class III/IV and for those unable to tolerate other therapies or needing combination 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,

Dr Janette Tenne

Medical Research Advisor

janette.tenne@researchreview.com.au

Inhaled combined budesonide-formoterol as needed in mild asthma

Authors: Beasley R et al.

Summary: This open-label trial evaluated the effects of inhaled budesonide-formoterol when used on an as-needed basis for mild asthma. 668 patients with mild asthma were randomised to receive inhaled albuterol as needed, regular inhaled budesonide plus albuterol as needed, or inhaled budesonide-formoterol as needed. The annualised exacerbation rate in the budesonide-formoterol as needed group was lower than that in the albuterol as needed group ($p<0.001$) and did not differ significantly from that in the regular budesonide group. The number of severe exacerbations was lower in the budesonide-formoterol as needed group than in both the albuterol as needed group and the regular budesonide group. The mean dose of inhaled budesonide was 107 µg/day in the budesonide-formoterol as needed group and 222 µg/day in the regular budesonide group.

Comment: In this open-label Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) trial, patients with mild intermittent asthma and persistent asthma were included. They were randomised into one of three treatments – albuterol only, budesonide maintenance or budesonide-formoterol as needed for symptom relief. The exacerbation rate per patient per year was lower in the budesonide-formoterol group compared to albuterol alone. Treatment with as-needed budesonide-formoterol was also superior to both albuterol alone and budesonide maintenance therapy in reducing the risk of severe exacerbations. The budesonide maintenance treatment was, however, superior in controlling asthma symptoms. Compliance with budesonide maintenance treatment was only 56%. This is an important trial, as it validates the results from the SYGMA trials in a real-world setting, raising the question whether current asthma treatment guidelines should be revised.

Reference: N Engl J Med 2019;380:2020-30

Abstract

Kindly Supported by

NURSES FOR NURSES NETWORK

AMA QUEENSLAND

Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH)

Authors: Sadushi-Kolici R et al.

Summary: Patients with CTEPH that was nonoperable or with persistent or recurrent PH after pulmonary endarterectomy were randomised to receive continuous subcutaneous treprostinil at target doses of ~30 ng/kg/min (high-dose; n=53) or ~3 ng/kg/min (low-dose; n=52) at week 12 in this phase 3 trial. Compared with the low-dose group, high-dose treprostinil was associated with a significantly greater improvement from baseline in marginal mean 6MWD by week 24 (44.98 vs 4.29 m; p=0.0016). In the high-dose group, there were 12 serious AEs affecting 10 participants, and in the low-dose group, there were 16 serious AEs affecting 9 participants. Pain and other reactions at infusion sites constituted most of the treatment-related AEs reported in both groups.

Comment: Pulmonary endarterectomy is the treatment of choice for patients with CTEPH, however, in many cases they may be inoperable and also about 16% of patients can have residual or recurrent pulmonary hypertension after surgery. Riociguat was approved for treatment of CTEPH based on the CHEST-1 trial and then in 2017 macitentan was approved for treatment of both treatment-naïve patients and in those already receiving other pulmonary arterial hypertension-targeted therapies. Previous studies on prostacyclin and other analogues have not been successful in CTEPH. This RCT looking at subcutaneous treprostinil in CTEPH showed significant improvement in 6MWD associated with improvements in pulmonary haemodynamics, functional capacity and BNP levels. Treatment was well tolerated and the most common AE was injection site reactions. These findings potentially offer patient with inoperable or residual pulmonary hypertension another treatment option.

Reference: Lancet Respir Med 2019;7(3):239-48
Abstract

The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity. A randomized, placebo-controlled, double-blind crossover trial

Authors: Taranto-Montemurro L et al.

Summary: This trial evaluated the effects of an oral combination of atomoxetine (a norepinephrine reuptake inhibitor) and oxybutynin (an antimuscarinic agent) on OSA severity and genioglossus responsiveness in patients with OSA. Twenty patients were randomised to receive placebo or atomoxetine 80 mg + oxybutynin 5 mg prior to sleep for 1 night each in a double-blind, crossover design. Median age was 53 years and BMI was 34.8 kg/m^2. Atomoxetine + oxybutynin decreased AHI by 63% compared with placebo (7.5 vs 28.5 events/h; p<0.001), and increased genioglossus responsiveness approximately 3-fold (6.3 vs 2.2 %/cmH_2O; p<0.001). Neither atomoxetine nor oxybutynin reduced AHI when administered separately in a subgroup of 9 patients.

Comment: The genioglossus (GG) muscle is one of the most upper airway dilators and loss of tone in the GG muscle during sleep is known to increase upper airway collapsibility. In animal models, the α_1 receptor agonist phenylephrine increased GG activity during wakefulness and NREM sleep, but GG muscle tone in REM sleep is regulated by muscarinic receptors with a significant increase in GG muscle tone by muscarinic blockers. Based on this experimental data, this study looked at the effect of combining a norepinephrine reuptake inhibitor and a muscarinic blocker. The results are very exciting, as this is the first significant advancement in the development of pharmacotherapy for OSA. In mild-moderate OSA, the drug combination did show a significant improvement in AHI. There was, however, a risk of reduced sleep efficiency, which is a known side effect of atomoxetine. Larger studies with longer duration are needed to see if the treatment effects are maintained and also to assess tolerability of the therapy.

Reference: Am J Respir Crit Care Med 2019;199(10):1267-76
Abstract

Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma

Authors: Khatri S et al.

Summary: Outcomes are reported from COLUMBA (Open-label Long Term Extension Safety Study of Mepolizumab in Asthmatic Subjects), which enrolled 347 patients with severe eosinophilic asthma who had participated in DREAM (Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma). In COLUMBA, all patients received subcutaneous mepolizumab 100 mg every 4 weeks plus standard of care until a protocol-defined stopping criterion was met. The average treatment duration was 3.5 years (a maximum of 4.5 years) and the total drug exposure was 1,201 patient-years. A total of 94% of the study cohort reported on-treatment AEs, resulting in an exposure-adjusted rate of 3,688 events/1,000 patient-years. The most frequently reported on-treatment AEs consisted of respiratory tract infection, headache, bronchitis, and asthma worsening. Around one-quarter (23%) of the cohort experienced ≥1 on-treatment serious AEs. Six deaths occurred during the study; none were attributed to mepolizumab. Among patients with ≥156 weeks on the study, the annualised exacerbation rate was 0.74 events/year (from baseline to week 156), a 56% reduction from the off-treatment period between DREAM and COLUMBA. At the first post-baseline assessment, the mean ACQ-5 score was reduced by 0.47 points and blood eosinophil counts were reduced by 78%.

Comment: This study reports on the results of an open-label, long-term extension in patients who participated in the DREAM study. The most common AEs reported with treatment were respiratory tract infections and headache. The most common serious AE was worsening of asthma. Rates of pneumonia were low and there were no cases of anaphylaxis. The study showed that exacerbation rates and asthma symptoms were significantly improved on treatment and these effects were maintained on treatment. The eosinophil counts were significantly suppressed on treatment, with no evidence of patients developing tolerance to mepolizumab. Immunogenicity findings were similar to previous studies, with low (<8%) antidrug antibodies.

Reference: J Allergy Clin Immunol 2019;143:1742-51
Abstract

Raw bioelectrical impedance analysis variables are independent predictors of early all-cause mortality in patients with COPD

Authors: de Blasio F et al.

Summary: Bioelectrical impedance analysis (BIA) uses specific predictive equations to estimate fat-free mass and fat mass in patients with COPD. Raw BIA variables such as high- to low-frequency impedance ratios (IRs) and phase angle (PhA) have been related to survival and various clinical outcomes in various diseases, but have not previously been investigated in COPD. These researchers sought to determine whether IR and PhA provide independent prognostic value for 2-year survival in a cohort of 210 patients with COPD. Impedance (Z) was obtained at 5 frequencies (5, 10, 50, 100 and 250 kHz) and PhA was obtained at 50 kHz. Three IRs were calculated: Z at 50 kHz/Z at 5 kHz (50/5 IR), Z at 100 kHz/Z at 5 kHz (100/5 IR), and Z at 250 kHz/Z at 5 kHz (250/5 IR). During 2 years of follow-up, all-cause mortality was 13.8%. Significant differences were observed between nonsurvivors and survivors in terms of age, weight, BMI, FEV_1, inspiratory capacity, and modified Medical Research Council dyspnoea score. With terms of nutritional variables, nonsurvivors had lower fat-free mass (p=0.031) and fat mass (p=0.015), higher IRs (p<0.001 for all the ratios), and lower PhA (p<0.001) compared with survivors.

Comment: Previous studies have shown a number of extrapulmonary factors that are independent risk factors associated with increased mortality risk in patients with COPD. Walking distance, physical activity and inflammatory markers have also been shown to be associated with clinical outcomes. Low skeletal mass and unintentional weight loss are known to be linked to survival. In this study, the predictive role of bioelectrical impedance analysis (BIA) was evaluated in regard to long-term survival in 210 consecutive patients with COPD with varying degrees of spirometric severity. Both the IR and PhA were used to assess body composition and were independently associated with all-cause mortality. Every percentage increase in IR was associated with a higher risk of mortality and with every unit decrease of PhA, the risk of death was 47% lower. The advantage of BIA is that it is noninvasive and can be performed in hospitalised patients with no requirement for weight or height and now has been shown to be a strong predictor of outcomes in COPD patients.

Reference: Chest 2019;155(6):1148-57
Abstract

Extended anticoagulation for VTE. A systematic review and meta-analysis

Authors: Mai V et al.

Summary: These researchers systematically reviewed the electronic literature from January 1990 through September 2018 for RCTs evaluating the effect of extended anticoagulation as secondary prevention for VTE compared with placebo. The analysis included 16 studies (12,458 patients). DOACs were associated with a reduction in overall (RR 0.48; 95% CI, 0.27 to 0.86; p=0.01) and VTE-related (RR 0.36; 95% CI, 0.15 to 0.89; p=0.03) mortality, whereas no such benefits were seen with VKAs. Although VKAs and DOACs prevented recurrent VTE by similar extents, only VKAs increased the risk of major bleeding (RR 2.67; 95% CI, 1.28 to 5.60; p<0.01), leading to an enhanced net clinical benefit for DOACs (RR 0.25; 95% CI, 0.16 to 0.39; p<0.01 for DOACs vs 0.46; 95% CI, 0.30 to 0.72 for VKAs; p<0.01; $P_{interaction}$ = 0.05).

Comment: The current recommendation to extend anticoagulation beyond 3–6 months has been shown to reduce the risk of VTE recurrence but has not been shown to improve survival. This meta-analysis showed that extended anticoagulation with DOACs was associated with reductions in overall and VTE-related mortality. Both VKAs and DOACs prevented recurrent VTE. DOACs again had a better bleeding profile compared to VKAs with lower risk of massive bleeding. Overall, DOACs were associated with an improved net clinical benefit compared with VKAs.

Reference: Chest 2019;155(6):1199-216
Abstract

Effect of combined β-lactam/macrolide therapy on mortality according to the microbial etiology and inflammatory status of patients with community-acquired pneumonia

Authors: Ceccato A et al.

Summary: This research group compared 30-day mortality of a β-lactam plus macrolide with that of a quinolone-based regimen in patients with CAP. The researchers also sought to determine whether stratifying patients by microbial aetiology of CAP and levels of systemic inflammation was related to this mortality benefit. Data were analysed from a cohort of 1,715 patients with CAP and known aetiology admitted to the Hospital Clinic of Barcelona between 1996 and 2016; 932 (54%) patients received a β-lactam plus macrolide and 783 (46%) received a fluoroquinolone ± a β-lactam. A β-lactam plus macrolide regimen was associated with lower crude 30-day mortality in the overall population (5% vs 8% for a fluoroquinolone ± β-lactam regimen; p=0.015), although when further analyses adjusted for a propensity score and baseline characteristics, the β-lactam plus macrolide combination was protective for mortality only in patients with a high inflammatory response (CRP >15 mg/dL) and pneumococcal CAP (adjusted OR 0.28; 95% CI, 0.09 to 0.93). No benefits in mortality were observed for patients without a high inflammatory response and pneumococcal CAP or for those with other aetiologies.

Comment: This was a single-centre study that looked at the mortality benefits of combined β-lactam and macrolide therapy in CAP. All patients had a confirmed bacterial pathogen. The majority of cases were pneumococcal pneumonia. The results showed that patients with pneumococcal pneumonia with raised inflammatory markers (CRP >15 mg/dL) had significant mortality benefits when treated with β-lactam+macrolide. The same benefits were not seen in patients with atypical pneumonia or other aetiologies. The reasons are unclear, but may be due to the small number of patients in these groups. However, it is clear that in patients with pneumococcal pneumonia, the addition of macrolide to β-lactam therapy has clinical benefits and improves outcomes.

Reference: Chest 2019;155(4):795-804
Abstract

The cost-effectiveness of corticosteroids for the treatment of community-acquired pneumonia

Authors: Pliakos EE et al.

Summary: These researchers examined the cost-effectiveness of the use of corticosteroids in the treatment of CAP. They constructed a decision-analytic model comparing the use of corticosteroids + antibiotics with that of placebo + antibiotics for the treatment of hospital inpatients with CAP. A base-case analysis revealed that the corticosteroid strategy resulted in savings of $US142,795 per death averted. In a probabilistic analysis, at a willingness to pay of $US50,000, the corticosteroid strategy had a 86.4% chance of being cost-effective compared with placebo + antibiotics. In cost-effectiveness acceptability curves, corticosteroid strategy was cost-effective in 87.6% to 94.3% of simulations for a willingness to pay ranging from $US0 to $US50,000. In patients with severe CAP (PSI classes IV/V), the corticosteroid strategy resulted in savings of $US70,587 per death averted and had a 82.6% chance of being cost-effective compared with the antibiotics-only strategy.

Comment: The clinical benefits of corticosteroids in CAP have been controversial and inconsistent across previous studies. This study assessed the cost-effectiveness of corticosteroids from previously published studies. It did show that in severe CAP (PSI classes IV and V) treatment with corticosteroids + antibiotics resulted in significant cost savings. The study also showed a slightly reduced mortality risk with corticosteroid treatment. These benefits were not seen in non-severe CAP. It is interesting to note that the majority of cost savings came from reduced length of hospital and ICU stay. It had no effect on readmission rates or duration of antibiotic treatment. More work is required for subgroups of patients such as the elderly, who have much higher mortality, even with less severe CAP.

Reference: Chest 2019; 155(4):787-794
Abstract

Prevalence of atrial fibrillation in hospital encounters with end-stage COPD on home oxygen

Authors: Xiao X et al.

Summary: This study analysed data from the 2003–2014 Nationwide Inpatient Sample in the US to evaluate the prevalence of AF in patients with end-stage COPD on home oxygen who were hospitalised for COPD exacerbation. 1,345,270 patients were included in the analysis. The prevalence of AF increased from 12.9% in 2003 to 21.3% in 2014 (p<0.0001). Advancing age, female sex, white race, high income, and large hospital size were associated with increased risk of AF. The presence of AF in patients with end-stage COPD was a risk predictor for in-hospital death, acute respiratory failure, invasive or noninvasive mechanical ventilation, acute kidney injury, sepsis and stroke.

Comment: Prevalence of AF in COPD patients is common with previous studies showing that patients with COPD have a >4-fold increased risk of AF. This retrospective study looked at the prevalence of AF in end-stage COPD patients from 2003 through 2014. The prevalence rate of AF in the cohort was shown to have steadily increased over that period to 21.3% by 2014. COPD patients with AF were shown to have worse outcomes, an increased risk of respiratory failure and need for ventilatory support and longer hospital stay with higher mortality. A positive finding of the study was the fact that even though prevalence rates of AF have been increasing, mortality in patients with COPD and AF has improved.

Reference: Chest 2019;155(5):918-27
Abstract

Respiratory Research Review™

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.

Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis

Authors: Fermont JM et al.

Summary: This systematic review of the electronic literature up to August 2018 identified 61 studies that assessed the association between selected biomarkers and clinical outcomes (i.e. mortality, exacerbation and COPD hospital admission) in patients with stable COPD. Biomarkers included 6MWD, heart rate, fibrinogen, CRP, white cell count (WCC), IL-6 and IL-8, TNF-α, quadriceps maximum voluntary contraction, sniff nasal inspiratory pressure, short physical performance battery, pulse wave velocity, carotid intima-media thickness and augmentation index. Shorter 6MWD and elevated resting heart rate, fibrinogen, CRP and WCC levels were associated with a higher risk of mortality. Pooled HRs were 0.80 (95% CI, 0.73 to 0.89) per 50 m longer 6MWD, 1.10 (95% CI, 1.02 to 1.18) per 10 bpm higher heart rate, 3.13 (95% CI, 2.14 to 4.57) per 2-fold increase in fibrinogen, 1.17 (95% CI, 1.06 to 1.28) per 2-fold increase in CRP and 2.07 (95% CI, 1.29 to 3.31) per 2-fold increase in WCC. Shorter 6MWD and elevated fibrinogen and CRP were associated with a higher risk of COPD exacerbation, while shorter 6MWD, higher resting heart rate, CRP and IL-6 levels were associated with COPD-related hospitalisation. Scant data were available regarding associations with musculoskeletal measures.

Comment: COPD is known to be a systemic disease and spirometry alone does not help to predict disease progression or prognosis in patients. This study is a meta-analysis of a number of cardiovascular and musculoskeletal biomarkers and their association with clinical outcomes. The study found that shorter 6MWD, higher resting heart rate, fibrinogen, CRP and WCC at baseline were associated with higher mortality risk over 6 months. Shorter 6MWD, CRP and fibrinogen were also associated with increased exacerbation risk. 6MWD is the most studied musculoskeletal marker, but information on other biomarkers is lacking, highlighting the need for further research in this area.

Reference: Thorax 2019;74(5):439-46
Abstract

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au.
Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Research Review publications are intended for Australian health professionals.
RESEARCH REVIEW™ The Australian Perspective — Since 2007

