Respiratory RESEARCH REVIEW™

Making Education Easy

Issue 169 – 2020

In this issue:

- Budesonide-formoterol reliever for adults with mild–moderate asthma
- Over-the-counter SABA overuse in Australia
- Economic and health burden of uncontrolled asthma in the US
- Damp, mouldy housing and early childhood acute respiratory infection admissions
- Continued loss of asthma control after epidemic thunderstorm asthma
- Short-term pollen exposure and allergic/asthmatic manifestation risk
- Asthma in the elderly: functional and clinical characteristics
- Azithromycin in severe asthma (AMAZES trial)
- Usability of mepolizumab autoinjectors for patient self-administration
- Exhaled volatile organic compounds discriminate between neutrophilic and eosinophilic asthma

Abbreviations used in this issue

AIR = anti-inflammatory reliever
ED = emergency department
FeNO = fractional exhaled nitric oxide
LABA/SABA = long/short-acting β-agonist
QOL = quality of life
RCT = randomised controlled trial
SMART = single inhaler maintenance and reliever therapy

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Welcome to this issue of Respiratory Research Review with the topic of asthma.

We are in the middle of a significant change in asthma management: based on high-quality evidence, we are moving away from β-agonist-based therapy. With increased primary- and secondary-care co-ordination, we can expect to realise the benefits of inhaled steroids, and hopefully, within a month or two, we will have biological agents available targeting type 2 inflammation.

Thomas Hill and Richard Beasley wrote a beautiful, sharp commentary on 'The history and future of short-acting beta$_2$-agonist therapy in asthma'. The review starts with the β-agonist use as part of Chinese herbal medicine, ma-huang (*Ephedra equisetina*). The commentary then covers other significant points in past β-agonist use until it arrives at our current evidence, that β-agonists are not recommended as monotherapy for mild asthma. The article is an excellent reminder of critical events like the spikes in mortality with isoprenaline, fenoterol and the US FDA-mandated LABA safety trial. The editorial quotes a paper suggesting that even when doctors intend to prescribe SMART (single inhaler maintenance and reliever therapy), more than 90% still prescribe a SABA some of the time. That, of course, is not single-inhaler therapy. Most adults should have a fast-onset LABA (eformoterol) coformulated with an inhaled steroid as AIR (anti-inflammatory reliever) therapy alone in mild asthma or as SMART in more severe asthma.

Inhaled steroids take centre stage in the article by Paul O'Byrne and colleagues: 'Asthma progression and mortality: the role of inhaled corticosteroids'. It is a curated selection of the best evidence of the natural history, lung function and mortality of asthma in childhood and adults; the changing concepts in asthma diagnosis, severity assessment and treatment; and their effects on asthma progression on mortality. You will be aware that our evidence for inhaled steroids in asthma is strong for reducing asthma progression, improving lung function and reducing mortality; however, frustratingly, it is lacking in demonstrating an effect on long-term lung function. That may be a function of the type of studies performed and the way we have selected articles; our new area of 'big data' may provide new insights, particularly as our statistical methodology improves.

Ian Pavord, Rahul Shrimanker and Nicola Hanania provided the most practical overview on an approach to the assessment of patients who are potentially suitable for biological treatment in the ERS monograph on severe asthma in chapter 18: 'Biologics targeting type 2 inflammation'. Written by clinicians for clinicians, it provides practical algorithms on when to refer patients, how to select blockers of T2 cytokines, what effects should be expected and what to do if the patient doesn't respond to therapy.

Just briefly, three valuable articles that didn't make it into this selection. 1) 'Treatment of hypertension in patients with asthma' (N Engl J Med 2019;81:2278–9), a precise review of a problem we face daily in clinical practice with practical suggestions of drug classes to choose. 2) 'Effects of asthma exacerbation during pregnancy in women with asthma: a population-based cohort study' (Eur Respir J 2020;55:1901335) based on more than 100,000 pregnancies providing deep insights and updates (we may have to pick this up in the August issue). Finally 3), the discussion on the 'Association between soft drinks consumption and asthma' (BMJ Open 2019;9:e029046). This systematic review and meta-analysis was positive, as previous studies have been. However, more chilling is the 'association between soft drink consumption and mortality in ten European countries' (JAMA Intern Med 2019;179:1479–90). Based on data of around 500,000 people, daily sugar-sweetened soft drink consumption versus less than once per month was associated with increased risks of stroke and heart attacks; these associations were equally as strong for the subgroup analysis of 50,000 people who consumed artificially sweetened soft drinks daily.

We hope you enjoy this selection and would like to thank you for feedback and comments; bearing in mind the last article, I am open for ideas on what to replace my diet coke with.

Kind regards,

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

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL)

Authors: Hardy J et al., on behalf of the PRACTICAL study team

Summary: This 52-week open-label RCT in adults with asthma examined the combination of budesonide with the fast-onset LABA-reliever formoterol (n=437) versus maintenance budesonide plus SABA-reliever terbutaline as needed (n=448). Severe exacerbations (systemic corticosteroids for ≥3 days or hospital/ED admission) were lower with budesonide-formoterol than with budesonide-terbutaline (0.119 vs. 0.172 per patient per year; relative rate 0.69 [95% CI 0.48, 1.00]). The most common adverse event was nasopharyngitis, occurring in 35% of budesonide-formoterol recipients and 32% of budesonide-terbutaline recipients.

Comment: This PRACTICAL (Personalised Asthma Combination Therapy: with Inhaled Corticosteroids and Fast Onset Long-acting β-agonist) study is the fourth, crucial piece of evidence of AIR therapy. We now have two randomised, placebo-controlled trials and two randomised real-life studies. SYGMA 1 and 2 were regulatory RCTs (Respiratory Research Review, issue 151). The Medical Research Institute of New Zealand has added two real-life studies: first Novel START (Respiratory Research Review, issue 163) confirming the benefit of AIR therapy in mild asthma. In this study, 70% of participants were taking regular inhaled steroids. A subgroup of 110 participants had electronic monitors and had an unprecedented adherence rate of 76%. **Bottom line: budesonide-formoterol as needed in patients with moderately severe asthma was more effective than regular budesonide and as-needed terbutaline.**

Reference: Lancet 2019;394:919–28
Abstract

Understanding reliever overuse in patients purchasing over-the-counter short-acting beta$_2$ agonists

Authors: Azzi EA et al.

Summary: This real-world, cross-sectional, observational study sought to characterise patients who purchase and use over-the-counter SABAs from Australian community pharmacies. Survey respondents included 412 individuals aged ≥16 years who had requested an over-the-counter SABA. Of these, 70.1% had used SABAs >2 times per week over the prior 4 weeks, and thus were classified as overusers, 73.6% reported not using a preventer every day and 81.6% reported their asthma had been diagnosed by a doctor. Compared with respondents without SABA overuse, significantly greater proportions of overusers reported: i) moderate-to-severe nasal symptoms (80.8% vs. 63.0% [p<0.001]); ii) a diagnosis of depression (11.1% vs. 5.7% [p<0.001]); iii) uncontrolled asthma (59.0% vs. 15.4% [p<0.001]); iv) oral corticosteroid use to manage worsening asthma symptoms (26.2% vs. 13.5% [p<0.01]); and v) visiting a doctor for their asthma in the prior 12 months (74.5% vs. 62.5% [p<0.01]).

Comment: Australians can purchase SABAs over the counter. Researchers from New South Wales worked with 18 pharmacies to invite customers who bought SABAs to participate in a structured survey. Only about 80% of the SABA users had doctor-diagnosed asthma. Most used meter-dosed inhalers, a third used more than four puffs of SABA a day over the last month and three quarters didn't use regular inhaled steroids. Patients who overused SABAs often had symptoms of rhinitis and were more likely to have needed a course of steroids in the last year. **Bottom line: purchasing SABAs over the counter is associated with suboptimal asthma control.**

Reference: BMJ Open 2019;9:e028995
Abstract

The projected economic and health burden of uncontrolled asthma in the United States

Authors: Yaghoubi M et al., for the Canadian Respiratory Research Network

Summary: Using a probabilistic model, these researchers estimated that the direct costs associated with uncontrolled asthma among American adolescents and adults over the next 20 years would be $US300.6 billion, and the total economic burden with indirect costs included was estimated to be $US963.5 billion. Uncontrolled asthma was also estimated to be associated with 15.46 quality-adjusted life-years lost for these individuals over the next 20 years.

Comment: The statistics applied are beyond my ability to appraise; however, the authors' principle questions to estimate the cost of asthma treatment itself and also the cost of uncontrolled asthma are logical. Essentially, they are asking how much cost could be saved and QOL improved if all adolescents and adults with asthma achieve symptom control over the next 20 years. **Bottom line: if a paradigm shift occurs in the US, they could save $300 billion on direct costs and another $660 billion in indirect costs associated with uncontrolled asthma. Research into adherence is as important as investments into novel therapies.**

Reference: Am J Respir Crit Care Med 2019;200:1102–12
Abstract

Damp mouldy housing and early childhood hospital admissions for acute respiratory infection

Authors: Ingham T et al.

Summary: Housing quality measures were compared between 188 NZ children aged <2 years hospitalised with acute respiratory infections (cases) and 454 unmatched children, either seen in general practice with acute respiratory infections not requiring admission or for routine immunisation (controls). Compared with controls, the likelihood of hospitalisation was increased for each unit increase in Respiratory Hazard Index score (odds ratio 1.11 [95% CI 1.01, 1.21]), although adjustments for season, housing tenure, socioeconomic status and crowding did weaken the association (adjusted odds ratio 1.04 [0.94, 1.15]), whereas each unit increase in damp-mould index score remained significantly associated after these adjustments (1.15 [1.02, 1.30]). The authors estimated that the rate of acute respiratory admissions could be reduced by 19% each year if these harmful exposures were addressed.

Comment: Our colleagues in Wellington have conducted this research using a kaupapa Māori research framework. A differentiating feature of this study was an independent, professional building assessment applying a Healthy Housing Index. They enrolled 188 cases and 454 controls, and demonstrated a dose-dependent relationship between the damp-mould index and admission for acute respiratory infections. Acute respiratory infection in preschool children accounts for 50% of GP consultations. **Bottom line: by addressing dampness and mould, about 20% of acute respiratory infection-related admissions could be avoided with a direct saving of $8 million a year.**

Reference: Thorax 2019;74:849–57
Abstract

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Continued loss of asthma control following epidemic thunderstorm asthma

Authors: Foo CT et al.

Summary: The symptomatology and behaviours of individuals affected by epidemic thunderstorm asthma were assessed using structured phone questionnaires in this 12-month prospective, observational Australian study; responses to 442 completed questionnaires were analysed. Ongoing asthma symptoms at follow-up were reported by 80% of respondents, of whom 28% were affected by asthma symptoms at least once per week. Respondents with a prior asthma diagnosis, those with current asthma and those with probable undiagnosed asthma were significantly more likely to report persistent asthma symptoms ($p<0.01$ for all). Prescriptions for preventer inhalers were reported by 53% of respondents, of whom 51% were adherent for ≥5 days per week. Urgent medical attention for asthma during the preceding year was reported by 16% of respondents, and 42% reported having a written asthma action plan.

Comment: Currently, Australia is still dealing with unprecedented bush fires and our thoughts are with them. In December 2016, Melbourne was affected by catastrophic epidemic thunderstorm asthma causing more than 3500 ED presentations, 35 admissions to ICU and ten deaths. In 2017, our Melbourne colleagues followed up 442 people with structured telephone questionnaires. They describe different phenotypes; e.g. 80% reported ≥1 episode of asthma symptoms in the 12 months after the thunderstorm asthma, and 28% had persistent symptoms, even though 43% had no prior asthma. **Bottom line: an episode of thunderstorm asthma changes asthma trajectory of individuals with both loss of control of asthma and persistence of *de novo* asthma.**

Reference: Asia Pac Allergy 2019;9:e35
Abstract

Short-term exposure to pollen and the risk of allergic and asthmatic manifestations

Authors: Kitinoja MA et al.

Summary: This was a systematic review of 26 studies reporting data on the short-term effects of pollen exposure on allergic and asthmatic manifestations, with 12 of these studies providing data suitable for meta-analysis. Each ten-grain per cubic metre increase in pollen exposure was associated with increased risks of lower respiratory symptoms (effect estimate 1.01 [95% CI 1.00, 1.02]), allergy/asthma symptoms (1.02 [1.01, 1.03]), upper respiratory symptoms (1.07 [1.04, 1.09]) and ocular symptoms (1.11 [1.05, 1.17]). There was no significant association detected between short-term pollen exposure and daily lung function.

Comment: Allergic rhinitis and asthma symptoms after exposure to pollen are, at the moment, more relevant than bushfires and damp houses. A group of Chinese researchers performed a high-quality meta-analysis on the available evidence of pollen and symptoms of allergic rhinitis and asthma. The general pollen size varies between 20 and 100µm, and the concentration can be between 0 and 1000 per suspended particulate matter of air. The authors found a dose-dependent relationship of about a 2% increase in ED presentations for every ten grains of pollen per cubic metre of air. **Bottom line: short-term exposure to pollen increases respiratory and ocular symptoms in allergic and asthmatic subjects.**

Reference: BMJ Open 2020;10:e029069
Abstract

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Is asthma in the elderly different? Functional and clinical characteristics of asthma in individuals aged 65 years and older

Authors: Curto E et al.

Summary: These authors reported differential clinical and functional characteristics for a retrospective population of 1713 patients with asthma from Spain stratified by age group. The predominant features among 471 elderly patients with asthma were female sex, fewer smokers, greater obesity, worse lung function and lower FeNO values ($p<0.01$ for all), and the most frequently associated comorbidity was gastro-oesophageal reflux. Patients aged <65 years received the highest doses of inhaled corticosteroids (60.8%). For the overall study population, 23.2% received omalizumab and 8.2% were corticosteroid-dependent. Patients aged 65–74 years represented the highest proportion of antileukotriene agent recipients (42.9%).

Comment: Asthma is often thought of as an illness of children and adolescents; however, with an ageing population, we can expect a higher prevalence of asthma in older people with higher comorbidity and mortality. In this snapshot of 1700 asthma patients, Spanish researchers focussed on about 500 patients above the age of 65 years. Overall, 68% were women, 15% had difficult-to-control asthma and about 10% were smokers. Almost half of all patients had coexisting rhinosinusitis. Patients above the age of 65 years had increased rates of obesity, gastro-oesophageal reflux disease, sleep apnoea and a history of smoking. **Bottom line: elderly patients tend to have more severe asthma, with more comorbidities.**

Reference: Asthma Res Pract 2019;5:2
Abstract

Efficacy of azithromycin in severe asthma from the AMAZES randomised trial

Authors: Gibson PG et al.

Summary: This was an analysis of participants with severe asthma from the AMAZES trial, which was a randomised 48-week comparison of low-dose azithromycin versus placebo. Compared with placebo, azithromycin was associated with significant reductions in asthma exacerbations for 211 participants meeting the American Thoracic Society and European Respiratory Society taskforce definition of severe asthma (1.2 vs. 2.01 per person-year; incidence rate ratio 0.63 [95% CI 0.41, 0.96]) with a significant reduction in the proportion of participants experiencing ≥1 asthma exacerbation from 64% to 49% ($p=0.021$). Similar benefits in the azithromycin arm were seen for participants poorly controlled with Global Initiative for Asthma step 4 treatment and those with International Severe Asthma Registry-defined severe asthma. Azithromycin recipients with severe asthma also exhibited a significant improvement in QOL ($p<0.05$). Azithromycin was well tolerated; the main adverse events were gastrointestinal symptoms.

Comment: We previously reviewed the AMAZES trial in Respiratory Research Review, issue 145, which demonstrated the efficacy of low-dose azithromycin in persistent asthma. This research group published two articles providing us with further data. The first is this subgroup analysis of the about 200 patients with severe, persistent asthma in which azithromycin reduced exacerbation rates and improved asthma control. The second is a study on the effect on the lung biome: 'Long-term azithromycin reduces *Haemophilus influenzae* and increases antibiotic resistance in severe asthma'. **Bottom line: low-dose azithromycin reduced asthma exacerbations and improved QOL in severe asthma; however, it increased macrolide resistance.**

Reference: ERJ Open Res 2019;5:00056-2019
Abstract

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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.

Usability of mepolizumab single-use prefilled autoinjector for patient self-administration

Authors: Bernstein D et al.

Summary: Patients aged ≥12 years with severe eosinophilic asthma (evaluable n=157) received self- or caregiver-administered subcutaneous mepolizumab 100mg via an autoinjector every 4 weeks for 12 weeks in this phase 3a study. For the first and third administered doses, which were observed in-clinic, ≥98% were successful, and the success rate for the second dose administered unobserved at home was ≥96%; these findings were confirmed by mepolizumab trough concentration and blood eosinophil count measurements. By the end of the study, ≥88% of participants stated that they were 'very' or 'extremely' confident regarding the correct use of the autoinjectors. The on-treatment drug-related adverse event rate was 3%, with no fatal adverse events recorded.

Comment: We anticipate that PHARMAC will fund mepolizumab for our patients with severe asthma and ongoing symptoms despite treatment with high-dose inhaled steroids and a second controller. We are confident that mepolizumab will improve asthma control and will have reflected on practical algorithms on when to refer patients and how to select blockers above (ERS monograph). One disadvantage is the need for monthly subcutaneous injections in a day clinic. This study mentions the availability of ELISA assays to measure mepolizumab concentrations and detectability of mepolizumab antibodies on two patients. **Bottom line: essentially, all patients/caregivers were able to self-administer mepolizumab at home without safety concerns.**

Reference: J Asthma; Published online June 28, 2019
Abstract

Exhaled volatile organic compounds are able to discriminate between neutrophilic and eosinophilic asthma

Authors: Schleich FN et al.

Summary: The utility of exhaled breath using endogenously generated volatile organic compounds as a surrogate marker of sputum inflammatory phenotypes was explored in this prospective study. In a discovery cohort of 276 patients with asthma, gas chromatography-mass spectrometry identified seven potential biomarkers. Four volatile organic compounds of interest to discriminate among asthma inflammatory phenotypes were confirmed (using comprehensive two-dimensional gas chromatography coupled to high-resolution time-of-flight mass spectrometry) in a replication cohort of 245 patients. Hexane and 2-hexanone had the highest classification performance in eosinophilic asthma; their accuracies were comparable with that of blood eosinophils and FeNO. Moreover, very good prediction of eosinophilic asthma was achieved using a combination of FeNO, blood eosinophils and volatile organic compounds (area under the receiver-operating characteristic curve, 0.9). Higher nonanal, 1-propanol and hexane levels were seen in neutrophilic asthma, and the classification performance for the combination of these for neutrophilic asthma was similar to that of FeNO or blood eosinophils in eosinophilic asthma.

Comment: Inhaled steroids and anti-IL-5 anti-inflammatory treatments are most effective in eosinophilic airway inflammation, whereas their effect on innate driven neutrophilic inflammation is rather weak. Sputum analysis is the best technique to identify inflammatory subtypes; however, it has not transitioned into clinical practice. This landmark study from Belgium/the Netherlands uses two cohorts of patients with asthma to first discover and then validate four volatile organic compounds using an 'electronic nose' to discriminate between various types of airway inflammation. Peter Sterk is putting the findings into perspective in his editorial and gives us the **bottom line: clinical tailoring of breathomics will enable precision medicine for type 2 and non-type 2 asthma.**

Reference: Reference: Am J Respir Crit Care Med 2019;200:444–53
Abstract