# Respiratory Research Review™

Making Education Easy

Issue 157 – 2019


## In this issue:



**Abbreviations used in this issue**
**FeNO** = fractional exhaled nitric oxide
**HR** = hazard ratio
**LABA/SABA** = long/short-acting β-agonist
**RCT** = randomised controlled trial

# Welcome to issue 157 of Respiratory Research Review.

Just as we are crafting this issue of Respiratory Research Review with the focus on asthma, the Nelson fires are burning, and it is quite possible we will see more bushfires this summer. In case one of us are asked to assist, the editorial review on 'Current clinical management of smoke inhalation injuries: a reality check' by Arietta Spinou and Nikolaos Koulouris seems rather pertinent. They group injuries as related to 1) thermal injuries, 2) chemical injuries and 3) systemic toxicity via carbon monoxide or hydrogen cyanide. The authors summarise practical schema on detecting the injuries and treatment suggestions, including humidified high-flow oxygen, airway clearance, and early mobilisation and rehabilitation.

'Underdiagnosis and overdiagnosis of asthma' is the title of a concise clinical review by Aaron, Boulet, Reddel and Gershon. Data from this well-balanced article continue the theme through many of the articles selected in this issue. The authors review the relevant literature giving convincing evidence that underdiagnosis is possibly the larger evil, as well as sensible advice on how to address both under- and overdiagnosis in our clinical practice. The GSK Paediatric Project Advisory Board and Committee give advice focused on diagnosis and management in children, including an action plan (Thorax).

Many of you will be aware of the updated technical standards. In 2017 the ERS published 'technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests', and in 2018 the ERS added the 'technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing'. Also, the reader may be interested in the excellent review of the evidence on 'The mode of action of anticholinergics in asthma'.

Finally, we like two editorials/viewpoints by our opinion leaders. Li Ping Chung, Mark Hew, Philip Bardin, Vanessa McDonald and John Upham have published a viewpoint on 'Managing patients with severe asthma in Australia: current challenges with the existing models of care'. The authors reflect on current models for difficult-to-treat and severe asthma, and make valid points for better integration and resource allocation. Richard Beasley and colleagues from Wellington pick up on our paradoxes in asthma management (Eur Respir J). First, they summarise the existing ones: 1) using β-agonists as first-line treatment for an inflammatory illness; 2) initially giving patients autonomy to manage with a SABA but then expecting them to change to fixed-dose regimens with further treatment; 3) switching from 'as-needed SABA' to minimising SABA use; 4) having different safety messages for SABAs and LABAs (don't use a LABA alone in asthma); and 5) dislocating patients' understanding of asthma control. Then they add five more paradoxes, which you can see here.

We hope you enjoy this selection. Thank you for the feedback and we look forward to your comments.

Kind regards


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## Thunderstorm asthma: revealing a hidden at-risk population

**Authors:** Clayton-Chubb D et al.

**Summary:** These researchers surveyed staff and volunteers regarding the nature and extent of respiratory symptoms among healthcare workers during the Melbourne epidemic thunderstorm asthma event; the survey was completed by 511 respondents, mostly female, from a potential pool of ~9000. Symptoms suggestive of asthma during the Melbourne epidemic thunderstorm asthma event were reported by 25.6% of respondents, among whom most did not seek professional medical help. Among respondents reporting symptoms, 43.9% and 73.5% had histories of asthma and allergic rhinitis, respectively. Strong predictors of symptoms included a history of allergic rhinitis (odds ratio 2.77 [p<0.001]), a history of asthma (1.67 [p=0.037]) and Asian ethnicity self-identification (3.24 [p<0.001]); predominantly being indoors did not protect against symptoms.

**Comment:** This article links into the review on 'Underdiagnosis and overdiagnosis of asthma'. In 2016, more than 3500 patients needed treatment for thunderstorm asthma overwhelming the health system and leading to ten deaths from asthma. This survey was performed among 9000 staff and volunteers of Eastern Health. The low response rate of 6% opens the study up to selection bias. Of the 500 staff who responded, more than half reported a history of atopy, including allergic rhinitis, and about a quarter experienced asthma symptoms during the thunderstorm. The authors' **bottom line: a background of allergic rhinitis or grass pollen allergy increases the risk of developing thunderstorm asthma.**

***Reference: Intern Med J 2019;49:74–8***
Abstract

## Antibiotic use in children with asthma

**Authors:** Baan EJ et al.

**Summary:** Rates, indications and types of antibiotic prescriptions were reported for retrospective cohorts of patients aged 5–18 years with and without asthma entered in the Dutch IPCI (Integrated Primary Care Information) database (946,143 person-years of follow-up) and the UK THIN (The Health Improvement Network; 7,241,271 person-years of follow-up). Children with asthma had higher recorded antibiotic use than nonasthmatics (197 vs. 126 and 374 vs. 250 per 1000 person-years for the IPCI and THIN cohorts, respectively); 14% and 4% of antibiotic prescriptions for the respective cohorts were for an asthma exacerbation only, and prescriptions among asthmatics were more frequently for lower respiratory tract infections compared with nonasthmatics (18% vs. 13% and 21% vs. 12% for IPCI and THIN, respectively). Age, gender and database had a greater impact than asthma status on drug type and quality indicators.

**Comment:** In this collaborative study between the UK and the Netherlands, the authors pooled prescribing data from 8 million person-years. Asthma was defined as having filled two prescriptions of asthma inhaler medication. The authors apply slightly complex statistics and conclude children with a background diagnosis of asthma are more likely to be prescribed antibiotics. One limitation of the study is that the real causes for antibiotic prescribing couldn't be identified. The authors speculate whether point-of-care C-reactive protein level testing may assist the diagnostic process. **Bottom line: antibiotics appear to be overprescribed in children with asthma.**

***Reference: BMJ Open 2018;8:e022979***
Abstract

## Prenatal antibiotic exposure and childhood asthma

**Authors:** Loewen K et al.

**Summary:** The relationship between prenatal antibiotic exposure and childhood asthma was explored in a population-based cohort study of 213,661 mother-child dyads from Canada. Prenatal antibiotic exposure was documented for 36.8% of the children, and 10.1% developed asthma. Compared with nonexposure, antibiotic exposure prenatally was associated with an increased asthma risk (adjusted HR 1.23 [95% CI 1.20, 1.27]), with an apparent dose response (1.15 [1.11, 1.18], 1.26 [1.21, 1.32] and 1.51 [1.44, 1.59] for 1, 2 and ≥3 antibiotic courses, respectively). Consistent with these findings, the risk of asthma in the children was significantly increased by maternal antibiotic use during the 9 months before pregnancy and the 9 months *post partum* (respective adjusted HRs 1.27 [95% CI 1.24, 1.31] and 1.32 [1.28, 1.36]).

**Comment:** Some evidence suggests antibiotic use during infancy alters gut microbiome and immune development, and is associated with an increased risk of childhood asthma (J Allergy Clin Immunol Pract). These Canadian authors present data on a population study of almost a quarter of a million mothers. Children exposed to antibiotics prenatally had a rate of asthma diagnosis of about 12 per 1000, while children without prenatal antibiotic exposure had a rate of about 9 per 1000 person-years. The authors carefully discuss this apparent 23% increase in asthma and are mindful of several limitations. **Bottom line: prenatal antibiotic exposure was associated with a dose-dependent increase in asthma risk.**

***Reference: Eur Respir J 2018;52:1702070***
Abstract

## Non-pharmacological management of adult asthma in Australia

**Authors:** Tan DJ et al.

**Summary:** This cross-sectional analysis of Tasmanian Longitudinal Health population-based cohort study data sought to explore the impact of nonpharmacological treatments for asthma on clinical measures in middle-aged adults. Of the entire cohort, 836 underwent clinical assessments including respiratory questionnaires and lung function testing in 2010. Of the 15.6% of the cohort who had asthma at the time of this analysis, 37.9% had seen a GP for their asthma and 16.5% had discussed their asthma with a pharmacist in the prior 12 months. Written and verbal asthma action plans were reported by 17.9% and 53.8% of participants, respectively, and 42.7% had received doctor assessments of inhaler technique. There was an increasing likelihood of a verbal asthma action plan as asthma severity increased (p=0.02 for trend), and patients with lower spirometry were significantly more likely to have received a verbal or written asthma action plan or inhaler technique education.

**Comment:** Patients greatly value discussions about nonpharmacological asthma management. Discussions are cost-effective and we have a good evidence base for them. Still, results from the Tasmania longitudinal health study seem to suggest that nonpharmacological asthma intervention use was low. Education of inhaler technique was high; however, this may be related to the good work of our pharmacist colleagues (Eur Respir J). Doctor assessment of inhaler technique, verbal management plans and written management plans were reported to have occurred in well below 50% of the cohort. This result may be affected by recall bias. **Bottom line: despite established evidence, nonpharmacological asthma interventions are underutilised in an adult asthma population.**

***Reference: J Asthma; Published online Dec 20, 2018***
Abstract

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## Passive nocturnal physiologic monitoring enables early detection of exacerbations in children with asthma

**Authors:** Huffaker MF et al.

**Summary:** Using a contactless bed sensor, nocturnal heart rate, respiratory rate, relative stroke volume and movement were recorded for 16 patients aged 5–18 years with asthma in this proof-of-concept study. Asthma symptoms and ACT (Asthma Control Test) scores were recorded every second week, and physiological parameters associated with asthma symptoms were determined using random forest modelling. The respective sensitivity and specificity values for the model were 47.2% and 96.3%, and it was 87.4% accurate, with heart rate and respiratory parameters the most important variables. Prediction of asthma symptoms on the day before perception of symptoms occurred 35% of the time; this increased to 100% for an individual subject for whom the model showed greater sensitivity. Heart rate and respiratory rate parameters were significantly associated with ACT score in multivariable and bivariable analyses.

**Comment:** In this proof-of-concept study, children with asthma were offered a wireless monitor, which was placed below the child's bedsheet and connected to the parent's Wi-Fi network. Based on only two measurements, heart rate and respiratory rate, as well as some derived variables, the attached algorithm was able to detect an asthma exacerbation 100% of the time, and in more than a third of cases before the recognition of symptoms by parents or children. **Bottom line: given the widespread use of wearable technology, eventually detection of exacerbations may assist asthma control.**

***Reference: Am J Respir Crit Care Med 2018;198:320–8***
Abstract



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## Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils)

**Authors:** Petsky HL et al.

**Summary:** This systematic review and meta-analysis included 16 clinically heterogeneous studies of FeNO-based management (seven in adults) and six of sputum-based management (five in adults) for tailoring asthma medications. Compared with controls, study participants who had been randomised to a sputum eosinophils strategy were significantly less likely to have ≥1 exacerbation (odds ratio 0.36 [95% CI 0.21, 0.62]), as were those randomised to a FeNO strategy (0.60 [0.43, 0.84] and 0.58 [0.45, 0.75] for adults and children, respectively); however, no significant group difference was seen for end-of-study daily inhaled corticosteroid dose, asthma control or lung function with either strategy.

**Comment:** Australian colleagues performed this meta-analysis combining data from three Cochrane reviews and updating their previous meta-analysis. Key findings are that neither FeNO nor sputum-based strategies could demonstrate an improvement in $FEV_1$, Asthma Control Questionnaire, quality of life, airway hyper-responsiveness or β-agonist use. After adding the newer studies, some benefit was seen in using FeNO in reducing exacerbations. Dominick Shaw asks in his editorial – 'FeNO monitoring to adjust treatment in asthma: has it come of age?' **Bottom line: FeNO reduces the likelihood of an asthma exacerbation, but has no significant impact on asthma control or lung function.**

***Reference: Thorax 2018;73:1110–9***
Abstract

## Prevalence, characteristics and management of frequently exacerbating asthma patients: an observational study in Sweden (PACEHR)

**Authors:** Janson C et al.

**Summary:** The prevalence, management and characteristics of frequent asthma exacerbations (≥2 exacerbations per year during a 3-year observation period) were reported for 18,724 Swedish adults with asthma. Frequent exacerbations during the year before the index date were reported for 6.43% of the patients, and frequent exacerbations yearly were reported for 1.8%. Compared with patients without exacerbations, those who experienced frequent exacerbations were older, were more often females and had elevated eosinophil and neutrophil counts, worse lung function and more comorbidities. Slight increases in asthma medication claims and slight decreases in physician visits compared with baseline were seen, regardless of frequent exacerbation status.

**Comment:** In NZ and in Sweden asthma is predominately treated in general practice. These Swedish researchers accessed their national primary care database with a unique personal identification number. Of the almost 20,000 patients with asthma, about 80% had no exacerbation in the last year and about 2% were exacerbation prone. These patients had a higher eosinophil count, a higher neutrophil count and lower baseline lung functions. They were also older, more likely to be female and had more comorbidities. **The authors' bottom line: these exacerbation-prone asthma patients with increased eosinophils may be the group to be targeted for treatment with biological agents.**

***Reference: Eur Respir J 2018;52:1701927***
Abstract

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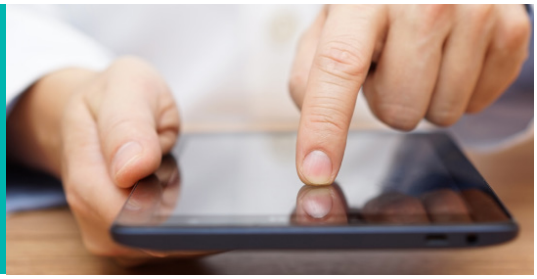

## Randomised controlled trials in severe asthma: selection by phenotype or stereotype

**Authors:** Brown T et al.

**Summary:** These researchers compared detailed characterisation data for a cohort of 342 patients with severe asthma against comprehensive trial eligibility criteria for 37 published phase 2B–3 RCTs evaluating a total of 20 biological therapies in severe asthma. Eligibility criteria for the phase 3 trials were met by 3.5–17.5% of the patients with severe asthma, with significant numbers excluded due to airflow obstruction, bronchodilator reversibility and smoking history criteria. Eligibility criteria excluded 73.2–86.6% of patients with severe eosinophilic asthma from participation in phase 3 licensing trials of therapies targeting IL-5 or its receptor.

**Comment:** This article needs to be appreciated with the accompanying editorial by Shrimanker, Beasley and Ciléin Kearns 'Letting the right one in: evaluating the generalisability of clinical trials'. The authors take their well-defined cohort of patients with severe asthma and systematically apply the inclusion criteria for 37 RCTs evaluating biological therapies. Only 10% would qualify to participate in these trials. Many fail because significant reversibility could not be demonstrated at the time of the trial. The (free) cartoon of the editorial should be our **bottom line: patients should be selected to trials not via diagnostic labelling, but via a 'treatable traits' approach.**

***Reference: Eur Respir J 2018;52:1801444***
Abstract

## Inflammation-dependent and independent airway remodelling in asthma

**Authors:** Elliot JG et al.

**Summary:** In this research, *post mortem* airway sections were taken from 51 asthma cases with and 29 without granulocytic inflammation in the inner airway wall, along with 48 nonasthmatic controls, and compared for estimated thickness of the airway smooth muscle layer, the basement membrane and inner and outer airway walls, as well as the size and number of airway smooth muscle cells, the volume fraction of extracellular matrix within the airway smooth muscle layer, airway smooth muscle shortening and luminal mucus. Compared with controls, cases with paucigranulocytic and those with granulocytic airway inflammation had increases in the thicknesses of the airway smooth muscle layer and basement membrane, and those with granulocytic airway inflammation also had increased inner and outer airway wall thickness and increased narrowing of the airway lumen due to airway smooth muscle shortening and mucus obstruction. Granulocytic inflammation was more frequent in fatal asthma cases.

**Comment:** In this study, researchers from Perth, Calgary, Sydney, Melbourne and Sao Paulo pooled *post mortem* data on patients with nonfatal asthma and fatal asthma. The 80 patients with asthma were divided into patients with a high degree of granulocytic inflammation who tended to have more evidence of airway inflammation with more mucus and more eosinophils, and patients with minimal granulocytic inflammation who had evidence of airway smooth muscle hypertrophy and signs of remodelling. The authors speculate that airway inflammation drives both processes. **Bottom line: basement membrane thickening and airway smooth muscle remodelling both have inflammation-dependent and inflammation-independent elements.**

***Reference: Respirology 2018;23:1138–45***
Abstract



## Treatable traits can be identified in a severe asthma registry and predict future exacerbations

**Authors:** McDonald VM et al.

**Summary:** These authors used the Australasian Severe Asthma Web-Based Database to attempt to identify treatable traits among 434 enrolees with severe asthma versus 102 with nonsevere asthma. There were able to identify 24 treatable traits, which were categorised as pulmonary, extrapulmonary and behavioural/risk factors. Compared with the nonsevere asthma population, the patients with severe asthma exhibited more pulmonary and extrapulmonary treatable traits, particularly allergic sensitisation, upper airways disease, airflow limitation, eosinophilic inflammation and frequent exacerbations. The strongest of the ten traits that predicted exacerbation risk were proneness to exacerbations, depression, inhaler device polypharmacy, vocal cord dysfunction and obstructive sleep apnoea.

**Comment:** In this article, our colleagues combine forces to identify treatable traits in severe asthma registries. I'd like to acknowledge Ben Brockway, David Langton, Richard Beasley, Jeff Garrett and Elaine Yap from NZ. In their graph, the authors summarise the key findings. Top of the 154 treatable traits are eosinophilic inflammation, an exacerbation-prone phenotype, inhaler device polypharmacy, obstructive sleep apnoea, depression, anxiety, allergic sensitisation and vocal cord dysfunction. The accompanying editorial gives us the **bottom line: the next step is to develop systems integrating this knowledge, enhance investigations and recommend a preferred treatment pathway.**

***Reference: Respirology 2019;24:37–47***
Abstract

### Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of 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 considering future collaborations.