

# Respiratory Research Review™

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Issue 163 – 2019

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### Abbreviations used in this issue

**COPD** = chronic obstructive pulmonary disease  
**ENDS** = electronic nicotine delivery system  
**FEF** = forced expiratory flow  
**FEV** = forced expiratory volume  
**FVC** = forced vital capacity  
**ICS** = inhaled corticosteroid  
**ICU** = intensive care unit  
**LABA/SABA** = long/short-acting  $\beta$ -agonist  
**NIV** = noninvasive ventilation  
**OR** = odds ratio  
**PFU** = plaque-forming unit

## Welcome to issue 163 of Respiratory Research Review.

"SABA [short-acting  $\beta$ -agonist]-only treatment is no longer recommended for treatment of asthma in adult and adolescents ... GINA now recommends that all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing controller treatment, to reduce the risk of severe exacerbations and asthma-related death" ([www.ginasthma.org](http://www.ginasthma.org)).

'GINA 2019: a fundamental change in asthma management', is the title of a short, free [editorial](#) in Eur Respir J that summarises the key recommendations, provides evidence and outlines the rationale for the changes. In essence, it comes down to the safety of ICSs, the lack of evidence for SABAs without steroids, and the danger of severe asthma exacerbations and asthma deaths when overusing SABAs.

The most solid evidence comes from the [START study](#), which was led by Richard Beasley and colleagues from the Medical Research Institute of New Zealand in Wellington. It builds on the SYGMA I and SYGMA II studies (Respiratory Research Review, [issue 151](#)), randomised controlled trials in patients that demonstrated that the as-needed combination product budesonide/formoterol was superior to salbutamol in improving asthma symptoms and asthma exacerbations in patients with mild asthma. As-needed budesonide-formoterol was also effective in controlling lung function and reducing exacerbation rates in patients with mild asthma, compared with regular ICSs. Both of these studies were performed in standard, rigid, randomised, placebo-controlled settings. The START study compared the use of as-needed single inhaler therapy with standard therapy. Standard therapy was either as-needed SABA or regular ICS therapy with as-needed SABA as per current guidelines.

The results of this trial are being communicated widely and you have likely heard the outcome in the national news, conference communications or research digests. Here are just three 'sound bites' of editorials in our major journals. "Replacement of as-needed SABA treatment with as-needed budesonide-formoterol or inhaled glucocorticoid maintenance therapy could reduce such [exacerbation] risk by approximately 50%." ([N Engl J Med](#)). "Frequent SABA use is associated with adverse asthma outcomes and evidence suggests replacing SABA with fast-acting LABA/ICS as reliever therapy reduces asthma exacerbation risk. We believe the time has come to move away from SABAs in asthma management" ([Eur Respir J](#)). And finally, Andy Bush in his [editorial](#) entitled 'Preventing asthma death: above all do no harm': "The second [reason] is that the blue inhaler is a killer; numerous asthma deaths occur in those who are using SABA for relief in increasing quantities but not using ICS".

As New Zealanders, we should enjoy the limelight with our Wellington and international colleagues. We hope you enjoy the selection of articles and we briefly wish to highlight two documents. One is an [editorial](#) reporting the remarkable success of controlling asthma in Finland, which essentially took a co-ordinated public health approach in providing anti-inflammatory medication to everybody diagnosed with asthma. Finally, we would like to acknowledge the amazing work Innes Asher from Auckland has done as the chair of the [Global Asthma Network](#). Asthma affects 339 million people and the Global Asthma Report 2018 connects us to the world, highlights challenges ahead of us, and is also greatly inspiring and solution focussed. It is beautifully produced, easy to read and might make you feel like a 'world citizen'.

Thanks for feedback, comments and emails; we hope you enjoy the selection of articles.

Kind regards,

**Professor Lutz Beckert**

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

## Controlled trial of budesonide-formoterol as needed for mild asthma

**Authors:** Beasley R et al., for the Novel START Study Team

**Summary:** This 52-week open-label trial evaluated the effects of as-needed inhaled budesonide-formoterol in 668 adults with mild asthma. Study participants were randomised to receive inhaled salbutamol as needed, regular inhaled budesonide plus salbutamol as needed or inhaled budesonide-formoterol as needed. The respective mean doses of inhaled budesonide in the as-needed budesonide-formoterol and regular budesonide groups were 107 and 222 µg/day. The annualised exacerbation rate among as-needed budesonide-formoterol recipients was lower than that for as-needed salbutamol recipients (relative rate 0.49 [95% CI 0.33, 0.72]) but not regular budesonide recipients (1.12 [0.70, 1.79]). As-needed budesonide-formoterol was associated with fewer severe exacerbations than as-needed salbutamol and regular budesonide (respective relative risks 0.40 [95% CI 0.18, 0.86] and 0.44 [0.20, 0.96]).

**Comment:** This study was performed in NZ and co-ordinated by the Medical Research Institute of New Zealand. We have summarised in the introduction the impact this study, the SYGMA studies (Respiratory Research Review, [issue 151](#)) and also the study by Alberto Papi has had. Papi and colleagues use beclomethasone/albuterol in a single inhaler for mild asthma and achieved similar results ([N Engl J Med](#)). The real strengths of this NZ study are the real-life conditions and electronic monitoring of all inhaler devices. **Bottom line: in patients with mild asthma, as-needed budesonide-formoterol was superior to salbutamol in preventing asthma exacerbations.**

**Reference:** *N Engl J Med* 2019;380:2020–30

[Abstract](#)

## Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight

**Authors:** Doyle LW et al., for the Adults born Preterm International Collaboration

**Summary:** This meta-analysis of individual participant data from 11 studies compared maximal expiratory airflow measured during late adolescence and early adulthood for 935 participants born very preterm or with very low birthweight versus 722 controls; the mean age at testing was 21 years. As expected, mean Z scores among control participants were close to zero, but very preterm or very low birthweight participants had reduced scores for FEV<sub>1</sub> (mean difference −0.78 [p<0.0001]), FVC (−0.25 [p=0.0012]), FEV<sub>1</sub>/FVC ratio (−0.74 [p<0.0001]) and FEF<sub>25–75%</sub> (−0.88 [p<0.0001]); similar patterns were seen when proportions of participants with values below the fifth percentile were compared.

**Comment:** “Adults with the first presentation of reduced lung function, in principle, could be caused by an acquired pathology (e.g. smoking) or they may have been born with small lungs.” Alvar Agusti and Rosa Faner articulate the lung function trajectories in health and disease in a beautiful comprehensive [article](#) in *Lancet Respir Med*. This meta-analysis adds to our knowledge by focussing on one special group. **Bottom line: individuals born very preterm or with a very low birthweight are at risk of not reaching their full airway growth potential and may be at increased risk of COPD in adulthood.**

**Reference:** *Lancet Respir Med* 2019;7:677–86

[Abstract](#)

## Prescribed analgesics in pregnancy and risk of childhood asthma

**Authors:** Shaheen SO et al.

**Summary:** Relationships between various analgesics prescribed during pregnancy and the risk of childhood asthma/wheeze were explored using linked Swedish health registry data for 492,999 individuals; negative paternal control and sibling comparison approaches were used to examine unmeasured confounding. Opioid, antimigraine drug and paracetamol (acetaminophen) use during pregnancy increased the likelihood of childhood asthma/wheeze risk across all ages once potential confounders had been accounted for; e.g. the respective ORs for asthma/wheeze at 4 years were 1.39 (95% CI 1.30, 1.49), 1.19 (1.01, 1.40) and 1.47 (1.36, 1.59). A paternal control analysis did not indicate the presence of unmeasured confounding by genetics or shared environment, but a sibling comparison analysis suggested that specific maternal factors confounded the aforementioned associations.

**Comment:** An association that has been suggested in several birth cohort studies is whether maternal paracetamol use is associated with preschool wheezing and childhood asthma. These authors chose a fascinating way to explore this association further. A randomised controlled trial in pregnant women would be hard to conduct. So, the authors turned to the national linked Swedish population database to look at medications prescribed to the mother and asthma in the child. They also explored siblings as controls because siblings share the family environment, maternal specific factors, and 50% of their segregating genes. **Their bottom line: analgesic use in pregnancy does not cause childhood wheeze or asthma.**

**Reference:** *Eur Respir J* 2019;53:1801090

[Abstract](#)

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## Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS)

**Authors:** Postma DS et al., on behalf of the ATLANTIS study group

**Summary:** The prospective ATLANTIS study, which recruited adults with (n=733) and without (n=99; controls) asthma from nine countries, evaluated combinations of biomarkers, physiological tests and imaging markers for measuring the presence and extent of small airways dysfunction. Structural equation modelling was applied to data from participants with asthma to assess the contribution of all physiological and CT variables to small airways dysfunction, from which clinical and CT scores for small airways dysfunction were defined. Participants with asthma were then classified into small airways dysfunction groups with model-based clustering, and asthma severity, control and healthcare use during the prior year were compared according to the scores and groups. All physiological measures contributed to the clinical small airways dysfunction model. Small airways dysfunction prevalence in asthma depended on the measure used – the lowest prevalence was associated with acinar airway ventilation heterogeneity ( $S_{acin}$ ). Impulse oscillometry and spirometry results were the greatest contributors to the clinical small airways dysfunction score and differed between the two groups. Group 1 (n=452) had milder small airways dysfunction than group 2 and comparable multiple breath nitrogen washout  $S_{acin}$  to controls, whereas group 2 (n=312) had abnormal physiological small airways dysfunction results, more severe asthma and higher clinical small airways dysfunction scores (which related to asthma control, severity and exacerbations) than group 1. No correlation was seen between clinical small airways dysfunction and CT small airways dysfunction scores.

**Comment:** This Assessment of Small Airways Involved in Asthma (ATLANTIS) study is a landmark study! It has always been plausible that small airways can become inflamed and contribute to asthma severity. There has been little consensus on the best measurement of small airways disease. These international researchers systematically recruited control subjects and asthmatics to investigate them with spirometry, CT scanning, body plethysmography, impulse oscillometry and multiple breath nitrogen washout tests. Reassuringly, our traditional measures perform well; however, the best picture is obtained by combining measurements. **Bottom line: small airways are involved in all patients with asthma, in particular, those with severe asthma.**

**Reference:** *Lancet Respir Med* 2019;7:402–16

[Abstract](#)

## Dynamic hyperinflation impairs daily life activity in asthma

**Authors:** van der Meer A-N et al.

**Summary:** These researchers explored associations between dynamic hyperinflation ( $\geq 10\%$  reduction in inspiratory capacity induced by standardised metronome-paced tachypnoea) and questionnaire scores (Asthma Control Questionnaire, Clinical COPD Questionnaire, St George's Respiratory Questionnaire, London Chest Activity of Daily Living and Shortness of Breath with Daily Activities) in 77 consecutive nonsmoking patients with moderate-to-severe asthma; dynamic hyperinflation was demonstrated in 81% of the patients. Relationships were detected between greater levels of dynamic hyperinflation and worse scores on all five questionnaires (r values 0.228–0.385 [ $p < 0.05$ ]). Only London Chest Activity of Daily Living and Shortness of Breath with Daily Activities remained significantly associated with dynamic hyperinflation after adjustment for asthma severity.

**Comment:** This physiological paper describes what happens when one can breathe in through inflamed airways yet finds it difficult to exhale, as the airways collapse as the intrathoracic pressure increases. The end result is dynamic hyperinflation, which these authors measured by asking patients with asthma to breathe at a metronome-paced frequency of twice their resting rate for 20 seconds. The inspired capacity performed immediately afterwards showed dynamic hyperinflation in 80% of all asthmatics, and the higher they scored on the severity questionnaire, the worse their hyperinflation was. **Bottom line: dynamic hyperinflation is associated with symptoms of severe asthma and should become a therapeutic target.**

**Reference:** *Eur Respir J* 2019;53:1801500

[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 with the view of future collaborations.




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**Reference 1.** Pharmac Schedule, [www.pharmac.govt.nz](http://www.pharmac.govt.nz), accessed 26 June 2019. **Xarelto® (rivaroxaban)** Prescription Medicine. Oral tablets containing 10 mg, 15 mg or 20 mg rivaroxaban. **INDICATIONS:** 1) For the prevention of venous thromboembolism in elective hip and knee replacement surgery. 2) Prevention of stroke and systemic embolism in non-valvular atrial fibrillation and at least one additional risk factor. 3) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE. Before prescribing Xarelto® please review the Data Sheet for information on dosage, contraindications, precautions, interactions and adverse effects. The Data Sheet is available at <https://medsafe.govt.nz/profs/Datasheet/x/Xarelto.pdf> or click **here** for abridged prescribing information. Bayer New Zealand Ltd. 3 Argus Place, Hillcrest, Auckland 0627. Xarelto® is a registered trademark of the Bayer Group, Germany. NZ-XAR-00180-07-2019 TAPS NA10853

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## Association of antibiotic treatment with outcomes in patients hospitalized for an asthma exacerbation treated with systemic corticosteroids

**Authors:** Stefan MS et al.

**Summary:** Associations of antibiotic treatment with outcomes were explored for a retrospective cohort of 19,811 adults who had been hospitalised for an asthma exacerbation and treated with systemic corticosteroids, among whom 44.4% were prescribed antibiotics. Compared with antibiotic nonrecipients, antibiotic recipients were older (median age, 48 vs. 45 years) and more likely to be white (48.6% vs. 40.9%) or smokers (6.6% vs. 5.3%), and they had more comorbidities. Antibiotic recipients also had a significantly longer median hospital stay (4 vs. 3 days) but a similar treatment failure rate (5.4% vs. 5.8%). A propensity score-matched analysis revealed that antibiotic treatment was associated with a 29% longer hospital stay and a greater median hospitalisation cost (US\$4776 vs. \$3641) with no difference in treatment failure risk (OR 0.95 [95% CI 0.82, 1.11]); similar results were seen after multivariable adjustments, propensity score weighting, an instrumental variable analysis and several sensitivity analyses.

**Comment:** This study was in over 500 US hospitals and comes under the topic of antibiotic stewardship; it also links back to my first ever clinical research suggesting that based on chest x-rays, patients admitted with asthma don't normally have pneumonia. The concern of missing an infection in a patient presenting with shortness of breath and discoloured sputum may be quite universal. The authors report that almost half of all patients admitted with asthma also received antibiotics, which were associated with a longer hospital stay, higher cost and increased antibiotic-related diarrhoea. **Bottom line: this research supports the current guidelines not to prescribe antibiotics in patients with an asthma exacerbation.**

**Reference:** JAMA Intern Med 2019;179:333–9

[Abstract](#)

## Non-invasive ventilation of patients with acute asthma

**Authors:** Sheikh M et al.

**Summary:** Outcomes were reported for seven ICU patients with acute asthma who received initial NIV (noninvasive ventilation), seven who did not receive initial NIV and eight who received invasive ventilation. Compared with patients who received invasive ventilation, those successfully managed with NIV alone required a shorter time in the ICU and hospital.

**Comment:** Frankston serves a population of about 40,000 people. This is a report on their admissions of patients with severe asthma to ICU, exploring the role of NIV in acute management. Of the 21 patients admitted, all survived and six were treated conservatively, seven with NIV, and eight needed intubation because of their severe metabolic compromise. The more intensive the treatment, the longer the stay in ICU and fewer complications patients experienced. **Bottom line: NIV could be considered as the first-line treatment for acute asthma; however, close observation in a high-dependency unit or ICU is recommended.**

**Reference:** Intern Med J 2019;49:262–4

[Abstract](#)

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ICS = inhaled corticosteroid, PRN = taken as needed. **References:** 1. Symbicort® Turbuhaler® Approved Data Sheet. 2. O'Byrne PM *et al.* *New Eng J Med* 2018; 378(20):1865–1876. 3. Bateman ED *et al.* *New Eng J Med* 2018; 378(20):1877–1887. Symbicort® and Turbuhaler® are trademarks of the AstraZeneca Group. Registered user AstraZeneca Limited, P299 Private Bag 92175, Auckland 1142. For Medical Information enquires: Telephone (09) 306 5650 or [medinfo.nz@astrazeneca.com](mailto:medinfo.nz@astrazeneca.com). To report an adverse event: Telephone (09) 306 5650 or via <https://aereporting.astrazeneca.com>. NZ-0891. TAPS DA 1939MC. 15688. August 2019. **AstraZeneca**

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## Tiotropium add-on therapy is safe and reduces seasonal worsening in paediatric asthma patients

**Authors:** Vogelberg C et al.

**Summary:** This was an analysis of a large safety database including five randomised, placebo-controlled studies, in which patients aged 1–17 years with symptomatic asthma received tiotropium 5µg or 2.5µg (n=1119) or placebo (n=572) as add-on therapy. Throughout the studies and for 30 days following treatment, reporting of adverse events was low and comparable across the study groups: tiotropium 5µg (51%), tiotropium 2.5µg (51%) and placebo (54%). Similarly, reporting of drug-related adverse events, those leading to discontinuation and serious adverse events was also low and did not differ significantly between treatment groups, regardless of age, disease severity or sex. Compared with placebo, tiotropium 5µg was associated with fewer adverse events relating to asthma symptoms and exacerbations, particularly during the seasonal peaks of these adverse events.

**Comment:** ICSs are the principle treatment for asthma. Despite treatment with ICS, more than half of asthmatics aged 4–18 years remain symptomatic. ICS therapy affects growth in children, so patients and doctors often explore add on therapy with LABAs, leukotriene receptor antagonists or tiotropium. This is a pooled analysis of more than 500 children receiving tiotropium versus placebo as add-on therapy. Tiotropium is not currently funded for asthma therapy in NZ. **Bottom line: added to ICSs, once-daily tiotropium is safe and reduces asthma symptoms and asthma exacerbations, in particular, seasonal peaks.**

**Reference:** *Eur Respir J* 2019;53:1801824

[Abstract](#)

## Secondhand exposure to aerosols from electronic nicotine delivery systems and asthma exacerbations among youth with asthma

**Authors:** Bayly JE et al.

**Summary:** These researchers examined the relationship of second-hand ENDS (electronic nicotine delivery system) aerosol exposure and asthma exacerbations among youth with asthma, using data from 11,830 individuals aged 11–17 years who participated in the 2016 Florida Youth Tobacco survey with a self-reported diagnosis of asthma. Around one-fifth (21%) reported having an asthma attack in the prior 12 months, and one-third (33%) reported second-hand ENDS aerosol exposure. In a multivariable logistic regression analysis controlling for covariates, second-hand ENDS aerosol exposure was associated with a higher likelihood of reporting an asthma attack (adjusted OR 1.27 [95% CI 1.11, 1.47]).

**Comment:** This epidemiological study is based on the Florida Youth Tobacco Survey with more than 70,000 participants. In this paper, the authors focus on the almost 12,000 youth aged 11–17 years. Of these, 21% reported an asthma attack in the last year, about 5% smoked tobacco and about 12% currently used ENDS. It has previously been shown that youth using ENDS had a higher likelihood of asthma diagnosis and asthma-related symptoms. The authors are careful to point out that their design doesn't allow any conclusion towards causality, still, **their bottom line: second-hand exposure to ENDS is associated with increased asthma symptoms in youth.**

**Reference:** *Chest* 2019;155:88–93

[Abstract](#)

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## Safety and tolerability of bacteriophage therapy for chronic rhinosinusitis due to *Staphylococcus aureus*

**Authors:** Ooi ML et al.

**Summary:** Nine adults with recalcitrant chronic rhinosinusitis with positive *Staphylococcus aureus* cultures sensitive to AB-SA01 (an investigational phage cocktail) received serial doses of twice-daily intranasal irrigations with AB-SA01  $3 \times 10^8$  PFUs for 7 days,  $3 \times 10^8$  PFUs for 14 days or  $3 \times 10^9$  PFUs for 14 days in this phase 1, first-in-human, open-label trial with a focus on safety and tolerability. There were no serious adverse events, deaths or changes in vital signs or biochemistry except for one recipient of the highest dose who experienced a decrease in blood bicarbonate level. There were six adverse events in total (all mild treatment-emergent events), all of which had resolved by the end of the study. Favourable outcomes were apparent in terms of efficacy across all cohorts, with two participants exhibiting clinical and microbiological evidence of *S. aureus* eradication.

**Comment:** This is a fascinating proof-of-concept study based on an idea that is more than 100 years old. Phages are viruses that only affect one bacterial species without pathogenic effects on mammalian cells; however, they have the ability to treat antibiotic-resistant bacteria and can penetrate biofilms. A total of nine patients participated in this study with twice-daily intranasal sinus lavages with a bacteriophage solution. The treatment was safe, well tolerated and may have a prolonged antibacterial effect. **Bottom line: bacteriophage treatment significantly improved symptoms of recalcitrant chronic rhinosinusitis.**

**Reference:** *JAMA Otolaryngol Head Neck Surg* 2019;145:723–9

[Abstract](#)

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