Welcome to issue 103 of Respiratory Research Review.

On World Asthma Day, the Healthcare Quality Improvement Partnership unit released its comprehensive review of asthma deaths in the UK with the title ‘Why asthma still kills’ ([http://hqip.org.uk/NRAD2014](http://hqip.org.uk/NRAD2014)). This report managed by the Royal College of Physicians reviewed the circumstances surrounding 195 asthma deaths in the UK in 2012/2013. The committee found ‘room for improvement’ in 83% of those who died. The expert panel identified factors that could have avoided death in relation to the health professionals’ implementation of asthma guidelines in 89 (46%) of the 195 deaths.

As a rough estimate, the committee felt that about half of the deaths were preventable. In particular, they reported that of the patients for whom severity could be estimated, 61 (39%) appeared to have severe asthma, 14 (9%) were being treated for mild asthma and 76 (49%) for moderate asthma. It is likely that many patients who were treated as having mild or moderate asthma had poorly controlled undertreated asthma, rather than truly mild or moderate disease.

NZ reported 65 asthma deaths with a disproportional burden of Māori and Pacific Island people. It may well be that about half of these deaths were preventable. The selection of articles in this issue of Respiratory Research Review focuses on identifying trigger factors, including viral infections and fungal spores. Most articles reviewed improvements in our management strategies. The ‘elephant in the room’ certainly is adherence to asthma treatment; it seems very likely that we will only make real progress if we learn to work together as healthcare delivery teams.

We hope you enjoy the selection. Any ideas on how to further care for our patients are greatly appreciated.

Kind regards

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Abbreviations used in this issue

ACQ = Asthma Control Questionnaire
CT = computed tomography
ED = emergency department
FENO = fractional exhaled nitric oxide
FEV = forced expiratory volume
ICS = inhaled corticosteroid

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Reference: 1. Pharmaceutical Schedule August 2014, PHARMAC
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Combination budesonide/formoterol inhaler as maintenance and reliever therapy in Māori with asthma

Authors: Pilcher J et al., SMART Study Group

Summary: In this study, 303 adults with asthma, 44 of who were Māori, were randomised to the single combination budesonide/formoterol inhaler as maintenance and reliever therapy (‘SMART’) or ‘standard’ regimen (combination budesonide/formoterol inhaler for maintenance and salbutamol as reliever) for 24 weeks. In analyses adjusting for ethnicity, the SMART regimen was associated with fewer days of ‘high use’ of reliever therapy (defined as >8 actuations of budesonide/formoterol in excess of four maintenance doses per day for SMART and >16 actuations per day of salbutamol for standard; relative rate 0.67 [95% CI 0.48, 0.94]) and fewer severe exacerbations (0.54 [0.36, 0.81]) compared with the standard regimen. The magnitude of the benefit from the SMART regimen was similar in Māori and non-Māori participants. Days of high use, days of high use without medical review and underuse of maintenance treatment were greater in Māori participants, regardless of treatment regimen.

Comment: These are further data from the SMART study reviewed last year (Respiratory Research Review issue 91). A strength of this study lies in its consultation with Māori researchers. This led to the inclusion of a Māori health provider at a Māori primary care health clinic, Tu Kotahi Māori Asthma Trust, and a 15% representation of Māori in this trial. Here the authors focussed on the subgroup of Māori patients, and found that Māori carried a higher disease burden. However, their bottom line: the Māori SMART group had a reduction in the number of high inhaler use days, a reduction of days without medical review and fewer severe exacerbations.


Airway inflammation and illness severity in response to experimental rhinovirus infection in asthma

Authors: Zhu J et al.

Summary: These researchers performed immunohistochemical analyses of inflammatory cells infiltrating the bronchial mucosa before and after experimental rhinovirus infection in 10 individuals with asthma and 15 without. Rhinovirus infection was associated with significant increases from baseline in epithelial and subepithelial neutrophil counts in asthmatics only. Significant increases in subepithelial CD8+ macrophages were seen after rhinovirus infection in all subjects, but the increase was greater in asthmatics. Positive associations were seen between CD45+, CD68+ and CD20+ cell and neutrophil and eosinophil counts at postinfection day 4 and virus load (r=0.50–0.72 [p=0.016–0.03]). Asthmatics also showed the following correlations at acute infection: i) CD4+ cells with chest symptom scores (r=0.69 [p=0.029]); ii) decrease in PEF, 10% fall in FEV1 with neutrophil count (r=−0.89 [p=0.029]); iii) PC20 inversely with CD4+ and CD8+ cell counts (respective r values −0.67 and −0.65 [p values 0.023 and 0.03]); iv) 20% fall in FEV1 inversely with CD20+ cell count (r=−0.65 [p=0.03]); v) higher epithelial CD8+ cell count with a greater maximum fall in FEV1, (r=−0.72 [p=0.03]); and vi) higher subepithelial mast cell count with a lower maximum percent fall in PEF (peak expiratory flow; r=0.8 [p=0.024]).

Comment: Rhinovirus infections are a strong trigger factor for acute exacerbations of asthma. These British researchers explored the mechanism after infecting participants with 10,000 units of rhinovirus via nasal spray and performing bronchial biopsies at baseline, 4 days and 6 weeks after infection. They described significant changes in the asthmatic group not seen in the controls and correlated them to spirometry and FENO measurements. The authors speculated that CD4 expression may have a protective effect. Bottom line: a viral dose-dependent increase in mucosal neutrophils, eosinophils and lymphocytes correlated with physiological measurements of asthma severity.


Abstract

CLICK HERE to read previous issues of Respiratory Research Review
Current asthma in schoolchildren is related to fungal spores in classrooms

Authors: Chen C-H et al.

Summary: These researchers surveyed 6346 parents of schoolchildren aged 6–15 years attending 44 schools across Taiwan, and measured fungal spores in classrooms, to assess allergic/asthmatic conditions. The respective prevalences of physician-diagnosed asthma, current asthma and asthma with symptoms reduced on holidays or weekends were 11.7%, 7.5% and 3.1%, and the respective geometric mean spore levels of total fungi, Aspergillus/Penicillium and basidiospores were 2181, 49 and 318 spores/m³. Significant correlations were seen between both Aspergillus/Penicillium and basidiospore levels and both current asthma and asthma with symptoms reduced on holidays or weekends after adjusting for personal and school factors. Symptom relief during the weekend was reported for 41% of children with current asthma.

Comment: One of the outcomes of the British review of asthma deaths is a lack of effort in identifying trigger factors. Taiwanese researchers went to great effort to explore the role of fungal spores in classrooms. They borrowed the concept of ‘asthma with symptoms reduced on holidays’ (ASROH) from occupational asthma. The researchers collected fungal spores for 40 min in the centre of each classroom with air samplers placed at the height of children’s respiratory zones in 44 schools. Their findings match the reports that reduced dampness in dwellings improves respiratory symptoms. Bottom line: a strong correlation between ASROH and high Aspergillus/Penicillium spore count has been observed.

Abstract

Effects of weight loss on asthma control in obese patients with severe asthma

Authors: Dias-Júnior SA et al.

Summary: This study involved patients with severe uncontrolled asthma and moderate obesity, 22 of who were randomised to undergo treatment for obesity; a further 11 served as controls. The bodyweight reduction programme was associated with a significant improvement in asthma control, as determined by a reduction in mean ACQ score from 3.02 at baseline to 2.25 at 6 months, whereas ACQ scores were unchanged in controls (2.91 at baseline and 2.90 at 6 months). This improvement was not accompanied by changes in markers of airway inflammation or bronchial reactivity, but by an increase in FVC (forced vital capacity).

Comment: The link between asthma and obesity is becoming clearer as both epidemics increase. Obesity probably affects asthma on several levels: a mechanical effect on the airways, an associated lack of fitness and the proinflammatory effect of ‘adipokines’ like leptin. Obesity-related asthma is associated with more severe disease, less response to steroids and worse clinical control. This group of Brazilian researchers reported on a cohort of patients who underwent a bodyweight reduction programme; about half of the patients managed to drop their weight significantly. Bottom line: weight loss leads to improved asthma symptoms without a change in FEV₁, or FENO.

Abstract

Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma

Authors: Wechsler ME et al., for the Asthma Intervention Research 2 Trial Study Group

Summary: The effectiveness and safety of bronchial thermoplasty at 5 years’ follow-up were reported for 162 participants from the Asthma Intervention Research 2 trial who had been treated with this therapy for severe, persistent asthma. Compared with rates during the 12 months before bronchial thermoplasty, the 5-year rates of severe exacerbations and ED visits were reduced by 44% and 78%, respectively, and had been consistently lower during each of the 5 years of follow-up. Respiratory-related adverse events and hospitalisations were similar for years 2–5 compared with the first year after bronchial thermoplasty. The average daily ICS dose decreased by 18% after bronchial thermoplasty, yet prebronchodilator FEV₁ values remained stable during this time. High-resolution CT scans revealed no structural abnormalities at year 5 that could have been attributed to bronchial thermoplasty.

Comment: About 5% of patients with asthma have severe, persistent symptoms despite optimal therapy. Bronchial thermoplasty delivered via a bronchoscope is thought to reduce smooth muscle hypertrophy. It has been shown to reduce exacerbations, ED visits, hospital admissions and time off school or work. Here the authors of the Asthma Intervention Research 2 trial reported their 5-year follow-up data, which included a scheduled repeat high-resolution CT scan. Despite a reduction in the steroid dose, the FEV₁, remained stable and exacerbations and ED visits continue to be reduced. Bottom line: bronchial thermoplasty can be added to the armamentarium for patients with severe, persistent asthma.

Abstract

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Effect of vitamin D₃ on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels

Authors: Castro M et al., for the National Heart, Lung, and Blood Institute’s AsthmaNet

Summary: The VIDA (Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma) trial randomised adults with symptomatic asthma and a serum 25-hydroxyvitamin D level of <30 ng/mL to receive oral vitamin D₃ 100,000IU followed by 4000 IU/day (n=201) or placebo (n=207) for 28 weeks added to inhaled ciclesonide 320 µg/day tapered to 160 µg/day for 8 weeks at week 12 if asthma control was achieved, then to 80 µg/day for 8 weeks if asthma control was maintained. No significant difference was seen between the vitamin D₃ and placebo arms for time to first asthma treatment failure during 28 weeks (composite of decline in lung function and increases in use of β-agonists, systemic corticosteroids and healthcare; primary outcome; 28% vs. 29%; adjusted hazard ratio 0.9 [95% CI 0.6, 1.3]). Of the nine prespecified secondary outcomes analysed, only the overall dose of ciclesonide required to maintain asthma control differed significantly between groups in favour of vitamin D₃ (111.3 vs. 126.2 µg/day).

Comment: Children and adults with asthma have been found to have low vitamin D levels. Low vitamin D levels create a pro-inflammatory state that has been linked to airway hyper-responsiveness, impaired lung function and increased exacerbations. Here, a team from leading US asthma researchers report on a placebo-controlled clinical trial of supplementing oral vitamin D in patients with asthma and low vitamin D levels to enhance steroid responsiveness and improve asthma control. The study may have been underpowered; however, their bottom line is: vitamin D supplementation did not significantly reduce the rate of treatment failure or asthma exacerbations.


Abstract

Multidisciplinary Approach to Management of Maternal Asthma (MAMMA)

Authors: Lim AS et al.

Summary: Pregnant women of <20 weeks’ gestation who had received antiasthma medications within the previous year were randomly allocated to a pharmacist-led intervention directed at improving maternal asthma control with multidisciplinary care, education and regular monitoring (n=29) or usual care (n=29). The intervention was associated with a significantly greater reduction in baseline ACQ score at 6 months compared with usual care (baseline-adjusted between-group difference –0.60 [p<0.001]), which was deemed to be clinically significant (>0.5). There were no reports of asthma-related oral corticosteroid use, hospital admission, ED visits or days off work.

Comment: This multidisciplinary team is addressing asthma management during pregnancy, as good asthma control is beneficial for the mother and the foetus. Despite the well-established safety of ICSs, about a quarter of doctors would instruct their pregnant patients to decrease or discontinue asthma medication during pregnancy when asthma was well controlled. This Melbourne study by pharmacists randomised pregnant asthmatic patients to an intervention including education, monitoring and feedback and a control group. Their main outcome measure was asthma control measured by the asthma control test. Bottom line: a multidisciplinary approach of asthma management leads to a significant improvement of asthma symptoms.

Reference: Chest 2014;145(5):1046–54

Abstract
**Medication use in Indian children with asthma: the user’s perspective**

**Authors:** Grover C et al.

**Summary:** This research sought to explore views on asthma medication use with semistructured qualitative interviews in 20 children with asthma and a parent/carer recruited from two Indian hospitals. The main issues reported were poor parent and child understanding of the disease and medications, with apparent fears, misinformed beliefs and lack of self-management skills. Themes that emerged from the interviews with the children included self-image, resistance to medication use and lack of responsibility in medication taking.

**Comment:** This is another study led by pharmacists, this time from Sydney in co-operation with the University of Delhi in India. A strong focus of asthma care is on compliance and educational interventions; however, not many studies have explored the child’s perspective. The authors used the qualitative tool of grounded theory methodology to explore the experiences of children and their caregivers regarding use of asthma medications. These results do not represent patients and doctors attitudes in our NZ culture; however, it highlights important aspects.


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**It’s the adherence, stupid (that determines asthma control in preschool children)!**

**Authors:** Kok T et al.

**Summary:** The relationship between ICS adherence and long-term asthma control was explored in 81 children aged 2–6 years with asthma using Smartinhaler® devices. The median adherence rate was 87%, and asthma was well-controlled during follow-up in 78% of the children. An association was seen between an adherence rate of >80% and better asthma control, with no important confounders identified. Lower adherence rates were significantly associated with persistent mild symptoms (p=0.028).

**Comment:** The results of the first study in this month’s Respiratory Research Review were based on data from the Nexus6 Smartinhaler, which sends data on metered-dose inhaler usage to a central site. This advice was also used by a group of Dutch paediatricians to explore the relationship between adherence to asthma treatment and asthma control. Knowing that adherence will be reported to a higher compliance rate with asthma therapy than in other studies. Still, as the title suggests, it was hardly surprising they came up with the **bottom line:** asthma care based on guidelines leads to well-controlled asthma – the key factor is adherence to ICS therapy.

**Reference:** Eur Respir J 2014;43(3):783–91

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**Abnormal vocal cord movement treated with botulinum toxin in patients with asthma resistant to optimised management**

**Authors:** Baxter M et al.

**Summary:** Eleven patients with optimised treatment-resistant asthma and abnormal vocal cord movement received a total of 24 botulinum toxin injections unilaterally into their vocal cords in this observational study. The treatment was associated with a significant improvement in asthma control test scores of 4.4 points (p=0.001) and a significant improvement in airway size on laryngeal CT (p=0.032), but no change in spirometric parameters. Adverse events were moderate (mainly dysphonia and dysphagia), although one participant experienced an asthma exacerbation.

**Comment:** We have previously commented on the results from Melbourne using a 320-slice laryngeal CT to detect significant upper airway/vocal cord dysfunction in patients with asthma (Respiratory Research Review issue 67). Laryngeal CT gives you images comparable with laryngoscopy. The group from Alfred identified a group of patients with asthma and laryngeal abnormalities. If optimising the treatment and speech language interventions were unsuccessful, the patients were offered unilateral botulinum toxin injection to the vocal cords. A placebo effect cannot be ruled out in this observational study. Bottom line: botulinum toxin injection led to an improvement of the asthma control test and airway diameter, but not FEV1.

**Reference:** Respirology 2014;19(4):531–7

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