Welcome to issue 121 of Respiratory Research Review.

"Is there still something new about asthma?" – you may well ask. We hope you enjoy this summer selection musings about asthma, and as always we hope for feedback, insights and shared experiences. In case you are not too time pressured, take a look at the UK audit on asthma death: Why asthma still kills; it has informed much of the recent research.

The asthma cohort study from Aberdeen makes fascinating reading; it has been following children with asthma for 50 years – many of them are now in their seventh decade of life. Peter Sly and Andy Bush wrote the accompanying editorial “From the cradle to the grave…”, in which they beautifully summarise the current state of the art of our thinking about the etiology of COPD. Not all patients who smoke develop COPD and not all patients with COPD have smoked. Some start adult life with small lungs. Peter Sly and Andy Bush suggest that suffering five factors of childhood disadvantage (namely childhood respiratory infection, parental smoking or a mother, father or child with asthma) places patients at least at a similar risk of developing COPD in later life as heavy smoking. This named cohort study reports that children with childhood asthma have a six times increased risk of developing COPD. With childhood factors being so important for later life, we are reviewing articles that may influence lung development like maternal stress in utero, maternal exposure to air pollution and exposure to traffic pollution in early life.

Another frontier in asthma care is patients with difficult-to-control asthma. Two research projects are likely to advance our thinking and management over the next few years: RASP-UK and U-BIORED. RASP-UK is starting from the premise that patients with severe asthma who fail to respond to corticosteroid therapy fall into three groups: i) nonadherence to steroid treatment (30–50%); ii) impaired response to steroids and ongoing high T2 eosinophilic inflammation (many newly characterised biological agents may be helpful here); and iii) nonresponsiveness to steroids with T2 low, neutrophilic asthma. The U-BIORED is a European consortium of 20 academic institutions, 11 pharmaceutical companies and six patient organisations with the objective of improving our understanding of the asthma disease mechanism using a systematic biological approach.

An article in Eur Respir J describes the first lessons learned from a cohort of 600 asthma patients. The best read for this is arguably the ‘Summary of the new GINA strategy: a roadmap to asthma control’ in which the authors, led by Helen Reddel, detail key changes in the updated GINA version. An example is the reflection on the term ‘asthma flare-up’ when communicating with patients. The medical term ‘exacerbation’ isn’t patient friendly and the term ‘attack’ is often misunderstood. The term flare-up conveys the concept of inflammation, and signals that asthma is present even when communicating with patients. The medical term ‘exacerbation’ isn’t patient friendly and the term ‘attack’ is often misunderstood. The term flare-up conveys the concept of inflammation, and signals that asthma is present even when symptoms are absent. This is a beautifully articulated document – a pleasure to read.

Research Review is ten!! The first ever issues of Research Review were delivered to inboxes in February 2006. Fast forward ten years and we now publish 48 regular reviews to which there are over 160,000 subscriptions. We’re grateful to each and every one of you for your support and are looking forward to even bigger and better things over the coming years.

Kind regards
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Abbreviations used in this issue
ACT = Asthma Control Test
COPD = chronic obstructive pulmonary disease
EIB = exercise-induced bronchoconstriction
FENO = fractional exhaled nitric oxide
FEV₁ = forced expiratory volume in 1 second
ICS = inhaled corticosteroid
OR = odds ratio
QoL = quality of life
RCT = randomised controlled trial

Reference:
1. Pharmaceutical Schedule April 2014, PHARMAC

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> ACT-based step-up regimen improves asthma control
> Repeated short education improves asthma control/QoL

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Reference:
1. Pharmaceutical Schedule April 2014, PHARMAC
Outcomes of childhood asthma and wheezy bronchitis

Authors: Tagiyeva N et al.

Summary: This paper reported 50-year outcomes for a cohort of 330 individuals, 38 of whom had childhood asthma and 53 had childhood wheezy bronchitis; among 239 controls, 57 developed adulthood-onset wheeze between the ages of 16 and 46 years. Adjusted multivariate analyses revealed that participants with childhood asthma and childhood wheezy bronchitis were significantly more likely to develop COPD (respective ORs 6.37 [95% CI 3.73, 10.94] and 1.81 [1.12, 2.91]), with the increased risks associated with reduced FEV1, evident by the fifth decade, rather than accelerated FEV1 decline, which was associated with adulthood-onset wheeze.

Comment: The average age of participants in the Aberdeen cohort, known as the WHEASE cohort, is now 61 years. After 50 years of following children with childhood asthma or wheeze in the presence of an upper respiratory tract infection, many participants are in their seventh decade of life. The authors confirm findings from the Melbourne cohort that children with childhood asthma are at 6-fold increased risk of developing COPD in adult life. The authors are able to extend on the findings from the Melbourne cohort. Bottom line: childhood asthma is associated with a 6-fold and childhood wheezy bronchitis with a 1.8-fold increased risk of developing COPD in adulthood.


Abstract

Prenatal particulate air pollution and asthma onset in urban children: identifying sensitive windows and sex differences

Authors: Hsu H-HL et al.

Summary: The impact of estimated prenatal exposure to particulate matter of ≤2.5μm in diameter in the development of childhood asthma was explored in 736 children born at ≥37 weeks’ gestation. Overall, distributed lag models, adjusting for child age, sex and maternal education, race/ethnicity (84% of mothers were from ethnic ‘minorities’), smoking, stress, atopy and prepregnancy obesity, revealed a significant association between particulate matter exposure during 16–25 weeks’ gestation and the development of early childhood asthma; sex-stratified analyses showed that a significant association was only present in boys.

Comment: In this study, the authors correlated exposure to air pollution based on satellite images with a diagnosis of asthma at age 6 years. They report an effect of in utero exposure to air pollution with an increased risk of developing asthma; an effect only observed in boys. The authors spell out their main weakness – they can’t confidently distinguish prenatal from postnatal exposure. The accompanying editorial points out that gestational exposure in animal models is associated with airway abnormalities. Bottom line: exposure to increased levels of air pollution during weeks 16–25 of gestation is associated with the development of childhood asthma.

Reference: Am J Respir Crit Care Med 2015;192(9):1052–9

Abstract

Prenatal maternal psychological stress and childhood asthma and wheezing

Authors: van de Loo KFE et al.

Summary: This was a meta-analysis of ten observational studies reporting on relationships between prenatal maternal psychological stress and childhood respiratory morbidity. The overall meta-analysis showed that children of mothers with some form of psychological stress during pregnancy had a higher prevalence of wheezing, asthma or other respiratory symptoms than those of mothers without psychological stress during pregnancy (pooled OR 1.56 [95% CI 1.36, 1.80]). Subgroup analyses of stress exposure, perceived stress, asthma and wheezing yielded similar findings.

Comment: When in utero exposure to air pollution has an adverse effect on lung development, what is the influence of maternal psychological stress during pregnancy on developing childhood asthma and wheezing? A group of Dutch researchers identified more than 10 studies on maternal stress during pregnancy, like the death of a husband, death of a child, exposure to violence or maternal depression. They concluded that future studies need to account for the impact of maternal psychological stress, because of their bottom line: children from mothers who suffered psychological distress during pregnancy had a 50% increased risk of developing wheeze, asthma and other respiratory symptoms.


Abstract

For more information, please go to www.medsafe.govt.nz

Reference: 1. Pharmaceutical Schedule August 2014, PHARMAC

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Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence

Authors: Gehring U et al.

Summary: Longitudinal associations between birth address air pollution exposure and the development of asthma and rhinoconjunctivitis throughout childhood and adolescence were explored in 14,126 participants from four European prospective birth cohort studies. The risk of incident asthma out to age 14–16 years was significantly increased with each 10 µg/m³ increase in NO₂ exposure (adjusted OR [95% CI 1.02, 1.25]) and by each unit increase in absorbance of particulate matter <2.5mm in diameter (1.29 [1.00, 1.66]), and there was a trend for increased risk with each 5 µg/m³ exposure to particulate matter <2.5m in diameter (1.25 [0.94, 1.66]) – these associations were more consistent after age 4 years. There was no evidence of an adverse relationship between air pollution and rhinoconjunctivitis.

Comment: The evidence that exposure to air pollution increases asthma symptoms and exacerbations flare-ups is strong. The question whether air pollution causes asthma will probably be answered in future cohort studies using personal air monitoring devices as the authors of the accompanying editorial suggest. In this study the authors used data from 14,000 participants from four cohort studies to approximate an answer. Their take-home message is that reduction in air pollution could help reduce childhood asthma because of their bottom line: exposure to air pollution increases the risk of developing asthma by age 14 years.

Abstract

Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years

Authors: Stockholm J et al.

Summary: Recurrent asthma-like symptoms lasting ≥3 days in 72 children were treated with oral azithromycin 10 mg/kg/day (n=79 episodes) or placebo (n=79 episodes) for 3 days in this RCT. Compared with placebo, azithromycin significantly shortened the mean duration of respiratory episodes after treatment (primary outcome; 3.4 vs. 7.7 days [p<0.0001]). Compared with starting treatment on or after day 6, starting before day 6 was associated with a significantly greater treatment benefit (3.4 vs. 7.7 days [p=0.001]). Clinical adverse events did not differ significantly between the azithromycin and placebo arms (p=0.30); post-treatment bacterial resistance patterns were not assessed.

Comment: The researchers of the Copenhagen Asthma in Childhood study had previously published that both viruses and bacteria were associated with asthma-like symptoms in the first 3 years of life. Backing their own observations, they now report on a RCT of azithromycin for wheezing in young children. Jonathan Grigg warns us in the accompanying editorial that this trial doesn’t justify the widespread use of azithromycin for troublesome respiratory symptoms; however, the bottom line is: azithromycin reduced the duration of asthma-like symptoms in young children either through antimicrobial or anti-inflammatory action.

Abstract

Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis

Authors: Di Bona D et al.

Summary: This was a systematic review and meta-analysis of RCTs comparing sublingual grass pollen immunotherapy tablets with placebo for seasonal allergic rhinoconjunctivitis. Small but significant benefits were seen with grass pollen sublingual immunotherapy for symptom score (13 RCTs; n=4658; standardised mean difference –0.28 [95% CI –0.37, –0.19]) and medication score (12 RCTs; n=4558; –0.24 [–0.31, –0.17]). The respective adverse event rates among sublingual immunotherapy and placebo recipients were 61.3% and 20.9%, and treatment-related adverse events requiring adrenaline (epinephrine) administration occurred in seven sublingual immunotherapy recipients.

Comment: Allergic rhinoconjunctivitis can be modified through the use of allergen-specific sublingual immunotherapy, which is widely used in Europe and has been licensed in the US since 2014. These Italian authors performed a meta-analysis on 13 trials reporting reduced patient symptom scores and 12 trials reporting reduced medication (antihistamine, prednisone) usage. Although the meta-analysis is mildly positive, the editor of JAMA Intern Med, Patrick O’Malley, warns us with the bottom line: the effect of specific sublingual immunotherapy is unimpressively small; 70% of the participants experienced side effects; the cost is substantial.

Abstract

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Exercise test using dry air in random adolescents: temporal profile and predictors of bronchoconstriction

Authors: Johansson H et al.

Summary: The temporal aspect of decline in FEV$_1$ following an exercise test while breathing dry air and EIB (exercise-induced bronchoconstriction) predictors were investigated in 99 adolescents with and 47 without self-reported exercise-induced dyspnoea. A positive EIB test (decline in baseline FEV$_1$ of ≥10%) was seen in 34% within 30 minutes, and was predicted by increased FENO, female gender and self-reported exercise-induced dyspnoea. Among participants with EIB, the greatest FEV$_1$ decline at 5–10 minutes after exercise was seen in 53% and the greatest decline at 15–30 minutes was seen in the remaining 47%.

Comment: One reason for respiratory problems while exercising is EIB. The BMJ published a beautiful clinical review explaining that EIB is more likely in people with asthma, but it also occurs in individuals without asthma. Because it can be confused with vocal cord dysfunction, a diagnostic workup should be considered. The Swedish authors of this study report on a sample of 146 adolescents with EIB, finding that female gender, increased FENO and self-reported exercise-induced dyspnoea predicted a positive test.

Bottom line: when performing exercise challenge testing in adolescents, lung function should be measured for at least 30 minutes.


Abstract

Improved criterion for assessing lung function reversibility

Authors: Ward H et al.

Summary: These researchers tested different bronchodilator reversibility criteria against the null hypotheses that there is no sex or size bias for bronchodilator reversibility, and determined the best criterion for defining bronchodilator reversibility with the hypothesis that clinically important bronchodilator reversibility should be associated with better survival in respiratory patients versus those without bronchodilator reversibility. First bronchodilator reversibility tests from 4231 patients with known subsequent survival status were used. Biases were seen for males and patients with larger baseline FEV$_1$ when bronchodilator reversibility was defined by absolute change and for those with lower baseline FEV$_1$ when defined by percentage change from baseline, whereas there was no size or sex bias when bronchodilator reversibility was defined by percent predicted. A multivariate Cox regression analysis showed survival advantages for patients with FEV$_1$ bronchodilator reversibility of >8% vs. ≤8% of predicted (hazard ratio 0.56 [95% CI 0.45, 0.69]). Patients with FEV$_1$ bronchodilator reversibility >8% predicted had better survival than those with FEV$_1$ bronchodilator reversibility <0, but not those with FEV$_1$ bronchodilator reversibility >14% predicted.

Comment: These British researchers reviewed the data on 4231 patients who underwent bronchodilator reversibility testing. Working on the hypothesis that patients with reversible airways disease (e.g. asthma) have better survival than patients with nonreversible airways disease (e.g. emphysema), they correlated the results of bronchodilator reversibility with mean survival. Men and people with a larger baseline FEV$_1$ had slightly better survival. They suggest an improvement of 8% in the FEV$_1$ may be the most appropriate criterion to define reversibility, because – bottom line – an improvement in FEV$_1$, of >8% predicted is associated with a significant survival advantage.


Abstract
Blood eosinophil count and prospective annual asthma disease burden

Authors: Price DB et al.

Summary: This analysis of anonymised medical record data from 130,248 UK cohort study participants from primary care explored the relationship between blood eosinophil count and asthma outcomes. Blood eosinophil counts >400 cells/μL, seen in 16% of the cohort, were associated with more severe exacerbations (adjusted rate ratio 1.42 [95% CI 1.36, 1.47]) and acute respiratory events (1.28 [1.24, 1.33]) and a lower likelihood of achieving overall asthma control (limited reliever use and no asthma-related hospital attendance/admission, acute oral corticosteroid course or antibiotic prescription; OR 0.74 [0.72, 0.77]) during the year after the most recent blood eosinophil count compared with patients with lower counts. As blood eosinophil count increased across nine categories, the exacerbation rate also progressively increased.

Comment: This international group led by David Price from Aberdeen identified about 130,000 patients with asthma who had an eosinophil count measured. The 20,000 patients who had an eosinophil count >400 cells/uL had significantly more severe exacerbations, acute respiratory events, worse overall asthma control as defined by reliever use, more asthma-related healthcare attendances and courses of prednisone. The cutoff of 400 cells/uL is well within the ‘reference range’ accepted by most laboratories.

Bottom line: asthmatics with a high eosinophil count are at risk of future exacerbation in addition to current GINA control status.


Abstract

Dedicated severe asthma services improve health-care use and quality of life

Authors: Gibeon D et al., on behalf of the British Thoracic Society Difficult Asthma Network

Summary: The relationships between systematic severe asthma assessment and both QOL and healthcare use were explored using data from a UK registry of 346 patients with severe asthma. Systematic severe asthma assessment significantly reduced healthcare use in terms of primary care or ED visits (66.4% vs. 87.8% [p<0.0001]) and hospital admissions (38% vs. 48% [p=0.0004]). There were also significant reductions in steroid dose (10 vs. 15mg [p=0.003]) and the proportion of patients needing short-burst steroids (77.4% vs. 90.8% [p=0.01]) despite no significant effect on requirement for maintenance oral corticosteroids. Systematic severe asthma assessment also had a significant positive impact on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores.

Comment: Asthma is, paradoxically, frequently underdiagnosed and undertreated and also often overdiagnosed and overtreated. The UK authors of the study above take great care to identify the 5–10% of asthmatics with difficult-to-control asthma despite good adherence to therapy. The authors report that among the 346 patients with severe asthma, a systematic, dedicated, multidisciplinary approach improves asthma outcomes as measured by a reduction in the use of healthcare services, improvements in QOL and Asthma Control Questionnaire. Bottom line: a dedicated severe asthma service centre is associated with improved QOL, asthma control and reduced healthcare use.


Abstract

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Cohort study of a simple ‘step-up’ regimen with the Asthma Control Test

Authors: Holt S et al.

Summary: This prospective NZ cohort study investigated the impact of simple guideline-based asthma management using an ACT (Asthma Control Test)-based ‘step-up’ regimen on asthma control in 93 primary-care patients with inadequately controlled asthma. The regimen was associated with good control (score >19) in 75% of the participants, with a mean ACT score increase of 6.0 (p<0.001) independent of baseline ICS (inhaled corticosteroid) use.

Comment: This short scientific letter details a study performed in a population of patients with asthma managed by NZ general practitioners. The authors tested the hypothesis that a stepwise increase of asthma medications improves asthma outcomes. All patients with an ACT score of <19 were offered an increase in their treatment from as-needed salbutamol to ICS plus salbutamol or from ICS to ICS/LABA (long-acting β-agonist). This simple intervention achieved asthma control, as defined by an ACT score of 19 or greater, in 75% of the patients, with a mean increase of 6 points. Bottom line: a ‘step-up’ regimen based on ACT scores results in improved asthma control.


A repeated short educational intervention improves asthma control and quality of life

Authors: Plaza V et al.

Summary: Adults with mild-to-moderate persistent uncontrolled asthma (n=230) were randomised by centre to an asthma educational programme based on repeated short interventions (four face-to-face sessions with administration of a written personalised action plan and training on inhaler technique at 3-month intervals) or usual clinical practice group for 1 year; specialised centres using a standard educational programme comprised a gold-standard group. While there were significant improvements in ACT scores in all three groups (p<0.001), compared with the usual clinical practice group, the intervention and gold standard groups had significantly greater increases (p=0.042) as well as fewer exacerbations and greater increases in QOL scores.

Comment: As Louis-Philippe Boulet points out in the accompanying editorial, education to self-manage asthma is an essential component in asthma management; however, it is met by barriers at patient, doctor and organisational levels. The above Spanish trial may be encouraging, as the authors report on a short (10-minute initial and 6-minute follow-up) intervention to deliver tailored, face-to-face asthma education for self-management. The authors showed a significant improvement in the ACT score. Bottom line: this short intervention may be able to bridge the gap between acknowledging self-management and enabling patients to manage their asthma themselves.


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