Welcome to this summer edition of Respiratory Research Review, when we take time to reflect on new insight into the possible causes of asthma as well as new treatment options.

It is more than 20 years since the ‘hygiene hypothesis’ was first articulated by Strachan (BMJ 1989;299[6710]:1259–60).

We begin the reviews with a 37-year review of a longitudinal study, which found that children with more infections in early life had less asthma. A study from Yale correlated a higher use of antibiotics in early life with a higher prevalence of asthma. Also, a lack of vitamin D was linked to more severe and less responsive asthma. All are generally supportive of the ‘hygiene hypothesis’.

Other authors investigated the idea that stress correlates with more severe asthma. A British study found that ‘mindfulness training’ significantly improved asthma-related quality of life. We finish the reviews with four studies looking at pharmacological asthma management. One study found no difference in asthma treatment failure using symptom-, physician- or biomarker-based strategies. The Dundee group described a better outcome when taking montelukast compared with a long-acting β-agonist in asthmatic children with Arg16β-receptors. We end the reviews with the ‘Best Paper in Respirology 2012’, describing an improvement of airway diameter with combination products.

As always we look forward to your comments and suggestions.

Kind regards
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In this issue:

- Childhood infections and asthma risk
- Early antibiotic exposure and subsequent asthma/allergy
- Childhood bronchial hyper-responsiveness predicts some adolescent asthma
- Effects of vitamin D and ICS treatment on children’s lung function
- Allostatic load biomarkers and adolescent asthma
- Mindfulness training and quality of life/lung function
- Strategies for adjusting ICS therapy
- Tailored second-line therapy in Arg16 children
- Airway dimensions with budesonide/eformoterol vs. budesonide alone
- Budesonide/eformoterol maintenance and reliever

Childhood infections and the risk of asthma

Authors: Burgess JA et al

Summary. This analysis of data from individuals followed over 37 years from childhood to middle age found the following individual negative associations: i) pertussis and asthma persisting to age 13 years (adjusted OR 0.53 [95% CI 0.28, 1.00]); ii) chickenpox and asthma persisting to age 32 years (0.58 [0.38, 0.88]); and iii) rubella and asthma persisting to ages 32 and 44 years (0.61 [0.31, 0.96] and 0.53 [0.35, 0.82], respectively). Significant associations were also seen between pertussis and preadolescent incident asthma (adjusted hazard ratio 1.80 [1.10, 2.96]), and measles and adolescent incident asthma (1.66 [1.06, 2.56]). Childhood pneumonia was significantly associated with current asthma at ages 7 and 13 years (adjusted ORs 3.12 [2.61, 3.75] and 1.32 [1.00, 1.75], respectively), particularly in individuals without versus with eczema (3.46 [2.83, 4.24] vs. 2.08 [1.38, 3.12]).

Comment. The authors of this study proudly reported on the findings from the 37-year follow-up of the Tasmanian Longitudinal Health Study of 8583 participants enrolled in 1968 at age 7 years. The authors found a lower asthma prevalence in adults who had the childhood infections chickenpox, rubella and mumps. Interestingly, childhood asthma prevalence was increased after infections with measles and pertussis. The authors reflect on a possible explanation in their discussion and endorse the current vaccination against childhood measles and pertussis, expressing the vision that it may reduce asthma burden in later life.

Bottom line: this study spanning four decades showed that childhood infections seem to protect against persisting asthma in later life.

Reference: Chest 2012;142(3):647–54


Abbreviations used in this issue

BSA = body surface area
FEV1 = forced expiratory volume in 1 second
ICS = inhaled corticosteroid
OR = odds ratio
PEF = peak expiratory flow

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Antibiotic exposure by 6 months and asthma and allergy at 6 years

Authors: Riesen KR et al

Summary: This analysis of data from a cohort of 1401 children found a significant relationship between antibiotic use during the first 6 months of life and the development of asthma/allergy by age 6 years (adjusted OR 1.52 [95% CI 1.07, 2.16]). In addition, associations were seen between antibiotic use and asthma/allergy in: i) children first diagnosed with asthma after age 3 years (1.66 [0.99, 2.79]); ii) children who had experienced a lower respiratory infection during the first year of life (1.66 [1.12, 3.46]); iii) children with no family history of asthma (1.89 [1.00, 3.58]); and iv) children with a positive allergy blood or skin test (1.59 [1.10, 2.28]).

Comment: These American authors investigated another aspect of the ‘hygiene hypothesis’. They argued that use of antibiotics in early childhood may alter the gastrointestinal flora and deprive the body of its opportunity to develop a healthy immune response resistant to allergic sensitisation. They used data from the PRAM (Perinatal Risk of Asthma in Infants of Asthmatic Mothers) study, excluding children with asthma prior to the age of 6 months to reduce ‘protopathic’ bias. They urge us to be careful when prescribing early antibiotics, particularly in children without genetic predisposition.

Bottom line: antibiotic use before age 6 months is associated with asthma and allergy at age 6 years.

http://aje.oxfordjournals.org/content/173/3/310.full

Does bronchial hyperresponsiveness in childhood predict active asthma in adolescence?

Authors: Riiser A et al

Summary: These researchers assessed the value of bronchial hyper-responsiveness to methacholine and exercise challenge at 10 years of age in 530 children for predicting active asthma 6 years later. Methacholine dose required to decrease FEV1 by 20% (PB20) and exercise-induced bronchoconstriction were associated with increased risks of subsequent asthma (β values 0.94 [95% CI 0.92, 0.96] per μmol of methacholine and 1.10 [1.06, 1.15] per percentage reduction in FEV1), with these tests explaining 10% and 7%, respectively, and 14% combined, of asthma variation at age 16 years. The area under the receiver operating characteristic curve for predicting asthma was greater for PB20 than for exercise-induced bronchoconstriction (0.69 vs. 0.60).

Comment: These American authors investigated another aspect of the ‘hygiene hypothesis’. They argued that use of antibiotics in early childhood may alter the gastrointestinal flora and deprive the body of its opportunity to develop a healthy immune response resistant to allergic sensitisation. They used data from the PRAM (Perinatal Risk of Asthma in Infants of Asthmatic Mothers) study, excluding children with asthma prior to the age of 6 months to reduce ‘protopathic’ bias. They urge us to be careful when prescribing early antibiotics, particularly in children without genetic predisposition.

Bottom line: antibiotic use before age 6 months is associated with asthma and allergy at age 6 years.

http://aje.oxfordjournals.org/content/173/3/310.full

Effect of vitamin D and inhaled corticosteroid treatment on lung function in children

Authors: Wu AC et al, for the Childhood Asthma Management Program Research Group

Summary: The effects of vitamin D levels on prebronchodilator FEV1, bronchodilator response and responsiveness to methacholine were assessed in 1024 children with persistent asthma; 65%, 25% and 10% were vitamin D sufficient, insufficient and deficient, respectively. Compared with vitamin D sufficient and insufficient children, those who were deficient were more likely to be older, have higher body mass index and of African American ethnicity. In children under treatment with ICSs (as part of the randomised Childhood Asthma Management Program), bronchodilator FEV1 increased by 140mL over 12 months in those who were vitamin D deficient, compared with 330mL and 290mL in those who were vitamin D insufficient and sufficient, respectively (p=0.0072).

Comment: This study from Harvard investigated a possible link between asthma prevalence and vitamin D deficiency, as both have dramatically increased. Some studies have already found lower lung functions in patients with vitamin D deficiency. These authors confirmed the finding that children with vitamin D deficiency have poorer baseline lung functions. When treated with ICSs, children with vitamin D deficiency had a rather poor response rate. Naturally this retrospective study cannot prove causality, and prospective, blinded randomised studies are ongoing. Bottom line: we don’t quite have enough evidence to prescribe vitamin D for asthma management.

http://ajrccm.atsjournals.org/content/186/6/508.abstract
Allostatic load biomarkers and asthma in adolescents

Authors: Bahreinian S et al

Summary: This prospective nested case-control study evaluated the susceptibility to asthma of preadolescents with ‘allostatic load’ ≥3 (a biomarker of chronic stress exposure) and adolescents. Children aged 7–10 years were recruited and followed until aged 11–14 years. Boys with high versus lower allostatic load had a 4-fold increase in asthma prevalence, with a similar increase seen in new-onset asthma (adjusted OR 4.35 [95% CI 1.19, 15.9]). In biomarker analyses, combinations of total cholesterol, glucose and cortisol levels were associated with similar or greater risks than total cholesterol level, high-density lipoprotein level, cortisol level, glucose level, dehydroepiandrosterone level and hip-to-waist ratio. The accompanying editorial is critical about the validity of the measurements (Am J Respir Crit Care Med 2013;187(2):115–6). Still, the authors’ bottom line is: boys with markers of allostatic stress have a 4-fold higher prevalence of asthma than boys with a normal allostatic stress level.

Reference: Am J Respir Crit Care Med 2013;187(2):144–52
http://ajrccm.atsjournals.org/content/187/2/144.abstract

Effect of mindfulness training on asthma quality of life and lung function

Authors: Pbert L et al

Summary: This study found that compared with an educational control programme (n=41), adults with mild-to-severe persistent asthma randomised to mindfulness-based stress reduction (n=42) experienced clinically significant improvements from baseline in Asthma Quality of Life Questionnaire scores (difference 0.66; p<0.001) and perceived stress scale scores (4.5; p=0.001), but not morning PEF, PEF variability, FEV1, or percentage of patients with well-controlled asthma. Bottom line: mindfulness training did not improve lung functions, but significantly improved asthma-related quality of life and stress in patients with asthma.

Reference: Thorax 2012;67(9):769–76
http://thorax.bmj.com/content/67/9/769.full

Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma

Authors: Calhoun WJ et al, for the Asthma Clinical Research Network of the National Heart, Lung and Blood Institute

Summary: The BASALT (Best Adjustment Strategy for Asthma in the Long Term) trial randomly assigned adults with mild-to-moderate asthma controlled by low-dose ICS therapy to adjustment according to physician assessment (n=114; dose adjusted every 6 weeks), exhaled nitric oxide (n=115; dose adjusted every 6 weeks) or symptoms (n=113; salbutamol [albuterol] rescue use). No significant between-group differences were seen for time to treatment failure, with 9-month failure rates of 22%, 20% and 15% for physician-, biomarker- and symptom-based adjustments, respectively.

Comment: The reader should consider studying this American National Heart, Lung and Blood Institute randomised, placebo-controlled, three-parallel-group trial of 342 adults with asthma. The authors demonstrated that none of the three possible treatments were superior when measuring time to loss of asthma control. Patients did just as well with physician-guided therapy as when adjusting their therapy with (expensive) biomarker measurement. Actually, they did just as well using their ICS based on symptoms and used significantly less inhalers. The editorial by O’Connor and Reibman (JAMA 2012;308[10]:1036–7) gives us the bottom line: we don't have enough evidence yet to change our management plans.

Reference: JAMA 2012;308[10]:987–97

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Tailored second-line therapy in asthmatic children with the Arg16 genotype

Authors: Lipworth BJ et al

Summary: These researchers randomised 62 children with persistent asthma who carried the homozygous Arg16 genotype to receive montelukast 5/10mg once daily or salmeterol 50/µg twice daily, added to inhaled fluticasone, for 1 year. Compared with salmeterol, montelukast was associated with significantly fewer school absences (primary outcome; p=0.005), significantly less use of salbutamol (p<0.001) and greater improvements in both symptom and quality of life scores, but no difference in FEV1.

Bottom line: adjusting therapy according to β-receptor genotype is a step towards personalised medicine.

http://www.clinsci.org/cs/124/0521/cs1240521.htm

Effects of budesonide/formoterol combination therapy versus budesonide alone on airway dimensions in asthma

Authors: Hoshino M & Ohtawa J

Summary: Patients with asthma (n=50) were randomly allocated to two inhalations of budesonide/formoterol 200/µg/6/µg or budesonide 200/µg twice daily for 24 weeks. Compared with budesonide alone, budesonide/formoterol was associated with: i) significantly greater decreases in airway wall area corrected for BSA (p<0.05), airway wall area percentage (p<0.001) and wall thickness/square root of BSA (p<0.05); ii) a significant increase in luminal area/BSA at the right apical segmental bronchus (p<0.05); iii) a reduction in sputum eosinophils; and iv) an increase in percent predicted FEV1. The changes in wall area percentage were significantly correlated with changes in sputum eosinophils and FEV1 in budesonide/formoterol recipients (respectively r values 0.84 and 0.64). Budesonide/formoterol was also associated with improvements in Asthma Quality of Life Questionnaire scores.

Comment: This paper from researchers in Japan was judged to be the Best Paper in Respirology 2012. The authors recruited 50 asthmatics with bronchial reactivity and randomised them to treatment with budesonide or treatment with the combination product of budesonide/formoterol. They used 1mm slice thickness CT scanning to assess the airway wall. After only 24 weeks, participants treated with the combination product had reduced airway thickness and eosinophilia and increased lung function and quality of life. Bottom line: treatment with budesonide/formoterol but not ICSs alone may modify progressive airway remodelling in asthma.

Reference: Respirology 2012;17(4):639–46

Budesonide/formoterol maintenance and reliever therapy via Turbuhaler versus fixed-dose budesonide/formoterol plus terbutaline in patients with asthma

Authors: Atienza T et al

Summary: Patients who had experienced ≥1 severe asthma exacerbation during the previous 12 months and were receiving maintenance ICS therapy (n=2091) were randomised to 12 months of treatment with a single inhalation of budesonide/formoterol 160/µg/4.5/µg twice daily plus as-needed inhalations of either the same combination or terbutaline 0.4/µg in this phase III study. There were 259 severe exacerbations involving 170 budesonide/formoterol maintenance/reliever recipients, and 363 exacerbations involving 229 budesonide/formoterol plus terbutaline recipients. Compared with budesonide/formoterol plus terbutaline, budesonide/formoterol maintenance/reliever therapy was associated with significantly longer times to first severe exacerbation (p=0.0007), first oral steroid use, first hospitalisation and first emergency room treatment, and a lower instantaneous exacerbation risk (hazard ratio 0.70 [95% CI 0.57, 0.85; p=0.0003]). Both treatments were well tolerated.

Comment: This randomised, double-blind, parallel-group study performed over 12 months is essentially addressing the question whether patients not well controlled on a combination product should increase their short-acting β-agonist or increase the combination product. This study has been recruiting patients from 13 countries, including Thailand, Philippines, Argentina and Japan. These results confirm the finding that the use of a rescue combination product reduced the exacerbation rate by 30%; it showed an improvement in lung function and asthma symptom scores. Bottom line: combination product baseline and adjustable combination product reliever therapy can be considered in some patients with asthma.