Welcome to issue 133 of Respiratory Research Review.

After a wait of more than 14 years, we finally have our own NZ adult asthma quick reference guide. Let’s make the most out of it after this long wait. The accompanying editorial suggests that this reference guide is user-friendly and has the potential to improve asthma outcomes, if we embrace it. A more detailed editorial in Respiriology highlights six aspects where the NZ guidelines differ from the Australian guidelines: i) diagnose asthma with increasing probability rather than a fixed spirometric cutoff; ii) apply the ACT (Asthma Control Test) to assess asthma symptoms; iii) prescribe inhaled steroids of 200–250µg fluticasone equivalents daily as the standard dose; iv) consider ICS/LABA as single therapy and adjustable rescue therapy (SMART) for patients at risk of severe exacerbation; v) use peak flow and FEV₁ as part of the initial assessment instead of oximetry; and vi) use lower dose inhaled salbutamol or ipratropium during exacerbations. Take a moment to have a look at the quick reference guide.

Do you remember the hygiene hypothesis debate? The principle idea was that a lack of early childhood exposure to infectious agents may predispose us to developing allergic diseases like asthma later in life. The clinical evidence base for this appealing theory had always been a little weak. Colleagues from the US present an amazing study comparing the asthma incidence in two farming populations. Both the Amish and the Hutterite originate from central Europe and have immigrated to the US where they remain reproductively isolated. The Amish employ traditional farming methods with a microbe-rich environment and an asthma prevalence of about 5%; the Hutterite employ modern, industrialised farming practices and report an asthma prevalence of about 21%. The N Engl J Med has also published an article from Denmark suggesting that fish oil ingestion in pregnant women may lead to a 30% reduction in persistent wheeze or asthma in the children from the treatment group. This is accompanied by a great editorial and an insightful ‘clinical decision’ making article on whether to start n-3 long-chain PUFA (polyunsaturated fatty acid) supplementation in pregnancy or not.

We review the evidence on a number of newly emerging treatment options of biological agents and a new prostaglandin receptor-2 antagonist in the management of persistent eosinophilic asthma. Also, colleagues from Canada remind us in the HUNT study that patients with asthma who engage in regular physical activity maintain their lung function better than inactive patients. We finish with a slightly depressing systematic review of errors in inhaler use; this Spanish/Danish collaboration reviewing 144 articles, reporting on more than 50,000 patients, demonstrates that there has been no evidence of improvement in inhaler technique over the last 40 years.

We hope you enjoy the selection of articles on the topic of asthma and will be looking forward to any feedback and comments. Kind regards

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Asthma and Respiratory Foundation NZ adult asthma guidelines: a quick reference guide

Authors: Beasley R et al.

Summary/comment: The GINA 2016 report is the benchmark in asthma care; however, with 147 pages, it is hard to access in daily practice. The NZ Reference Guide manages to distil the key information down to about 12 pages and some easily accessible tables, figures and asthma action plans. As we outlined in the editorial, with eight deaths under the age of 45 years and a total of 63 deaths from asthma in 2015, there is room for improvement. The guidelines identify evidence-based areas like: a) assessment of risk of severe exacerbations; b) the higher burden of disease in Māori; c) reduction of β-agonist overdose including considering single inhaler therapy for patients at high risk; and d) the use of written management plans. Bottom line: the adult asthma quick reference guide is brief, user-friendly and, if used, has the potential to improve asthma care.

Abstract

Innate immunity and asthma risk in Amish and Hutterite farm children

Authors: Stein MM et al.

Summary: Environmental exposures, genetic ancestry and immune profiles were investigated in 60 Amish and Hutterite children, with allergen and endotoxin levels measured and microbiome composition of indoor dust samples evaluated. Compared with the Hutterite children, the Amish children had asthma and allergic sensitisation prevalences that were 4 and 6 times lower, respectively, despite 6.8-fold higher median household endotoxin levels and similar genetic ancestries and lifestyles. There were also differences in household dust microbial composition, and in proportions, phenotypes and functions of innate immune cells. A murine model of experimental allergic asthma revealed significant inhibition of airway hyper-reactivity and eosinophilia on intranasal instillation of dust extracts from Amish homes, but not from Hutterite homes, with the protective effects abrogated in mice that were deficient in molecules critical for innate immune signalling (i.e. MyD88). The Amish children expressed a more innate-type immune response. The potential to improve asthma care.

Comment: This publication from colleagues in the US is based on 30 Amish and 30 Hutterite children, six with asthma. The researchers provide important proof-of-concept data that growing up in an environment with higher microbial exposure, documented by a 7-fold increase in endotoxin levels from airborne dust, may lead to less asthma. The researchers performed elegant experiments exposing peripheral blood lymphocytes to lipopolysaccharides. The Amish children expressed a more innate-type immune response. Also, dust samples from Amish households suppressed the induction of airway inflammation in a mouse model. Bottom line: farm dust and particular endotoxin exposure may have a protective effect against developing asthma.

Abstract

Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring

Authors: Bisgaard H et al.

Summary: Pregnant women were randomised at 24 weeks’ gestation to receive n-3 long-chain PUFAs 2.4g in the form of fish oil or placebo (olive oil) each day, with their children (n=695) prospectively followed for 3 years. Compared with children of mothers enrolled in the placebo group, a lower proportion of those of mothers from the n-3 long-chain PUFA group experienced persistent wheeze or asthma (primary endpoint; 16.9% vs. 23.7%; hazard ratio 0.69 [95% CI 0.49, 0.97]), with the effect appearing to be stronger for children of mothers with blood eicosapentaenoic acid and docosahexaenoic acid levels in the lowest tertiles at randomisation (17.5% vs. 34.1%; 0.46 [0.25, 0.83]). Maternal n-3 long-chain PUFA supplementation was also associated with a lower risk of lower respiratory tract infections among the children (31.7% vs. 39.1%; hazard ratio 0.75 [95% CI 0.58, 0.98]), but did not significantly affect their asthma exacerbations, eczema or allergic sensitisation.

Comment: Danish researchers randomised pregnant women at 24 weeks’ gestation to receive 2.4g of fish oil or olive oil in capsules per day. Children of mothers who took the fish oil supplements rich in n-3 long-chain PUFAs had a reduction in the diagnosis of persistent wheeze or asthma by about a third. Christopher Ramsden details in his editorial that the fish oil may shift the balance from pre-inflammatory mediators like leukotrienes to protective mediators like protectin or resolvin. The journal also presents a case vignette of a woman approaching you asking for your opinion on whether to take fish oil. Bottom line: fish oil supplementation during pregnancy may prevent asthma in childhood.

Abstract

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Fevipiprant, a prostaglandin D₂ receptor 2 antagonist, in patients with persistent eosinophilic asthma

Authors: Gonem S et al.

Summary: Patients from a single centre with persistent, moderate-to-severe asthma and a sputum eosinophil count of ≥2% were stratified by oral corticosteroid use and bronchoscopy and randomised to receive oral fevipiprant 225mg (n=30) or placebo (n=31) twice daily for 12 weeks, followed by a 6-week placebo washout period. (Placebo was incorrectly administered to one participant from the fevipiprant group throughout the trial, and to another at one mid-treatment visit; both were included in the fevipiprant group for the intent-to-treat primary analysis, but the former was assessed as a placebo recipient for the safety analyses.) Compared with placebo, fevipiprant was associated with a significantly greater geometric mean reduction from baseline in sputum eosinophil percentage (4.5- vs. 1.3-fold [p=0.0014]). The safety profile of fevipiprant was good, with no deaths or serious adverse events.

Comment: The last article suggested that fish oil may reduce the production of leukotriene, while this article explores the effect of the prostaglandin receptor, fevipiprant, on sputum eosinophil percentage as a marker of asthma airway inflammation. In a single-centre study at Glenfield Hospital, famous through its educational video, the authors report on a randomised control study of 60 participants showing an almost 5-fold reduction in sputum eosinophil counts with a favourable safety profile. Symptom control appeared to have improved; however, further studies and comparison with standard treatment with inhaled steroids are required (BMJ 2016). Bottom line: this new leukotriene antagonist looks promising in early studies.


Acetaminophen versus ibuprofen in young children with mild persistent asthma

Authors: Sheehan WJ et al., for the NIH/NHLBI AsthmaNet

Summary: This study investigated the association of as-needed use of paracetamol (acetaminophen) versus as-needed use of ibuprofen with asthma-related morbidity among children aged 12–59 months with mild persistent asthma. The 300 participants were randomised to receive paracetamol 160mg or ibuprofen 100mg per 5mL of a grape-flavoured suspension as needed to relieve fever or pain during a 48-week period. The paracetamol and ibuprofen groups did not differ significantly for: i) mean number of asthma exacerbations (0.81 vs. 0.87 per participant [p=0.67]); ii) the rates of ≥1 and ≥2 asthma exacerbations (49% vs. 47% and 21% vs. 24%, respectively); iii) the percentage of asthma-control days (85.8% vs. 86.8% [p=0.50]); iv) salbutamol rescue inhaler use (2.8 vs. 3.0 inhalations per week [p=0.69]); v) unscheduled healthcare utilisation for asthma (0.75 and 0.76 episodes per participant [p=0.94]); or vi) adverse events.

Comment: Asthma is more prevalent in Anglo-Saxon countries than in other parts of the world. One possible explanation for the increased prevalence of asthma may be the preferred use of paracetamol in the US and UK compared with other European countries. Observational studies suggest an association between paracetamol use and asthma. This prospective randomised controlled trial of paracetamol or ibuprofen in young children with asthma lets us take ‘a small sigh of relief’ (editorial). However, the trial design does not allow us to comment on whether paracetamol or ibuprofen causes asthma. Bottom line: paracetamol was no worse than ibuprofen in children with asthma.


Latrophilin receptors: novel bronchodilator targets in asthma

Authors: Faiz A et al.

Summary: Transcriptional differences between asthmatic and healthy airway smooth muscle cells from humans were investigated in culture. The research suggested that latrophilin receptors were increased in airway smooth muscle cells obtained from asthmatics compared with nonasthmatics both in vivo and in vitro. A latrophilin-1 gene single-nucleotide polymorphism was found to be associated with asthma and greater latrophilin-1 expression in lung tissue. Activated latrophilins were also found to regulate airway smooth muscle cell adhesion and proliferation in vitro, and promoted airway and airway smooth muscle cell contraction in mice.

Comment: Our colleagues from Holland report a potentially important hypothesis-generating study based on cultures of airway smooth muscle cells harvested from the airways of patients with asthma and healthy controls. Latrophilin receptors release acetylcholine and regulate smooth muscle adhesions, and proliferation leads to airway narrowing in mice. Using genome-wide gene expression techniques, the authors identify that enhanced expression of the latrophilin receptor type with a single-nucleotide polymorphism is more common in participants with asthma. Bottom line: activation of the latrophilin receptor seems to cause an asthma-like airway response; the receptor may become a therapeutic target in the future.

The effect of cigarette smoking on lung function in young adults with asthma

Authors: Hancock RJ et al.

Summary: This research followed a population-based birth cohort until age 38 years to investigate the effects of smoking and asthma on the development of airflow obstruction. Childhood-onset persistent asthma was reported for 91 patients, late-onset asthma for 93 and asthma in remission for 85, with 572 nonasthmatic participants making up the remainder of the cohort. Cumulative tobacco smoking histories and spirometry data were obtained at ages 18, 21, 26, 32 and 38 years. Both smoking history and childhood-onset persistent asthma were associated with lower FEV1/FVC ratios, with the associations between smoking and FEV1/FVC ratio differing according to asthma phenotype (p<0.001 for interaction). Associations were seen between smoking and lower pre- and postbronchodilator FEV1/FVC ratios among nonasthmatic participants and those with late-onset or remittent asthma, but not childhood-onset persistent asthma.

Comment: Smoking is the most common cause of fixed airflow obstruction, but it can also be caused by asthma. The prevalence rate of smoking in asthmatics is similar to that of the general population. Our colleagues from Dunedin are asking the question of whether smoking leads to accelerated decline in lung function and works synergistically with asthma to cause airflow obstruction. The authors report that about a third of children with asthma have persistent airflow obstruction and they also confirm that smoking causes airflow obstruction. However, contrary to their hypothesis, their bottom line is: participants with childhood asthma were not more vulnerable to the effects of smoking than participants without asthma.

Reference: Am J Respir Crit Care Med 2016;194(3):276–84

Severe asthma exists despite suppressed tissue inflammation

Authors: Wilson SJ et al.

Summary: The U-BIOPRED study compared bronchial immunopathology data for 158 participants, including adult nonsmokers and current/past smokers with severe, steroid-treated asthma, adults with mild or moderate asthma and healthy controls. Immunohistochemical biopsy analyses revealed that the healthy controls had more submucosal mast cells than the severe asthmatic nonsmokers, the severe asthmatic current/past smokers and the mild or moderate asthmatics (33.6 vs. 17.4, 22.2 and 21.2 per mm², respectively [p<0.01]), while the current/past smokers had less CD4+ lymphocytes than the severe asthmatic nonsmokers, mild or moderate asthmatics and healthy controls (4.7 vs. 11.6, 10.1 and 10.6 per mm², respectively [p<0.008]). An affymetrix microarray analysis identified seven probe sets in bronchial brushing samples with positive relationships with submucosal eosinophils.

Comment: We have reported before from ‘Unbiased Biomarker for the Prediction of Respiratory Disease Outcomes’ (U-BIOPRED), a research co-operation involving 20 academic centres, 11 ‘pharma’ partners and six patient organisations, which will expand our understanding of asthma over the next few years. The researchers performed comprehensive biological sampling, including bronchial biopsies on a large cohort of 96 patients with asthma and 41 healthy volunteers. From this they report on seven genes associated with eosinophilia. One key finding of this study is our bottom line: severe asthma exists despite suppressed endobronchial inflammation within the proximal airways, suggesting that an additional mechanism in the peripheral airways may contribute to asthma severity.


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.

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please CLICK HERE to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

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Physical activity and lung function decline in adults with asthma

Authors: Brumpton BM et al.

Summary: The population-based cohort HUNT study from Norway estimated annual mean decline in lung function in 1329 participants with asthma over mean follow-up of 11.6 years, and related these to weekly physical activity data obtained via questionnaire. For the respective inactive and active participants, the mean declines in FEV1 were 37 and 32 mL/year (difference –5 mL/year [95% CI –13, 3]), the mean declines in FVC were 33 and 31 mL/year (–2 mL/year [–11, 7]), the mean declines in FEV1/FVC ratio were 0.36% and 0.22% per year (–0.14% per year [–0.27, –0.01]), and the mean declines in peak expiratory flow were 14 and 10 mL/year (–4 mL/year [–9, 1]).

Comment: The region of Nord-Trøndelag in Norway has a population of just over 130,000. In 1984 they invited the entire population aged 20 years or older to participate in a population-based study. Here the authors report on the effect of exercise on lung function decline over about 12 years in about 1300 people with asthma. Participants who were active for >3 hours per week had a loss in their FEV1 of about 26mL per year compared with inactive participants, who had a loss of about 36mL per year in their FEV1. Bottom line: participants who were physically active for about 3 hours per week had a slower decline in their FEV1 and peak flow.

Reference: Respirology 2017;22(2):278–83

Abstract

STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma

Authors: Morton RW et al.

Summary: Ninety children aged 6–16 years with asthma poorly controlled with ICSs and LABAs had a commercial electronic monitoring device attached to their regular inhaler and were randomised to receive daily reminder alarms and feedback on ICS use (intervention) or usual care with adherence monitoring alone (device alarm disabled; controls). Compared with the control group, the intervention group exhibited significantly greater adherence (70% vs. 49% [p=0.001]) and required significantly fewer oral steroid courses and hospitalisations, but with no significant effect on change in Asthma Control Questionnaire score at 1 year.

Comment: The National Review of Asthma Deaths, ‘why asthma still kills’, reports that poor adherence was a contributing factor in about a third of patients who died of asthma. These authors explore the utility of electronic monitoring devices, which can provide reminder alarms, feedback to the patients and data to the researcher. Using the NZ ‘smart-inhalers’, both groups were monitored and only the intervention group received alarm reminders and electronic feedback. Asthma control test scores improved in both groups. Bottom line: the adherence in the group with electronic reminder alarms and feedback rose to 70%, they required fewer courses of oral steroids and had less hospital admissions.

Reference: Thorax; Published online Nov 4, 2016

Abstract

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Factors associated with failure of emergency department management in children with acute moderate or severe asthma

Authors: Ducharme FM et al., for the DOORWAY research group of the Pediatric Emergency Research in Canada (PERC) network

Summary: This prospective, multicentre research included 973 children aged 1–17 years treated with oral corticosteroid and severity-specific inhaled bronchodilator therapy on ED presentation with moderate or severe asthma (Pediatric Respiratory Assessment Measure score 4–12). The primary outcome of management failure (hospitalisation, ED therapy for ≥8 hours or relapse ≤72 hours following ED discharge with hospitalisation or prolonged ED stay) occurred in 17% of the children. Factors associated with management failure included virus detection (odds ratio 1.57 [95% CI 1.04, 2.37]), fever (1.96 [1.32, 2.92]), each 1-point increase in Pediatric Respiratory Assessment Measure score (1.38 [1.22, 1.56]), oxygen saturation <92% (3.94 [1.97, 7.89]) and presence of symptoms between exacerbations (1.73 [1.13, 2.64]), but not age, salivary cotinine level or oral corticosteroid dose. Compared with older children, preschoolers had higher rates of virus detection (67% vs. 46% [p<0.0001]) and fever (31% vs. 16% [p<0.0001]). There was also an association identified between virus detection and reduced speed of recovery over 10 days postdischarge.

Comment: Our colleagues from Canada report on the DOORWAY study of five paediatric EDs focussing on about 1000 children who presented with moderate to severe asthma. Under study conditions, 92% received oral steroids and 81% bronchodilators within an hour. Management failure occurred in 17% (165) of the participants. In preschoolers, a higher fever was associated with treatment failure. Virus detection, particularly of rhinovirus C and enterovirus D68, was also associated with an impaired response to steroids.

Bottom line: severity of the exacerbation, high fever, asthma symptoms between episodes and virus detection were associated with failure of ED management of asthma.


Systematic review of errors in inhaler use: has patient technique improved over time?

Authors: Sanchis J et al., on behalf of the Aerosol Drug Management Improvement Team (ADMIT)

Summary: This was a systematic review of data extracted from 144 articles reporting on 54,354 patients who underwent 59,584 observed tests of asthma inhaler technique. The most frequent metered-dose inhaler errors were to do with co-ordination (45%), speed and/or depth of inspiration (44%) and omission of postinhalation breath-hold (46%), and the most frequent errors with dry powder inhalers were incorrect preparation (29%), lack of full expiration before inhalation (46%) and omission of postinhalation breath-hold (37%). The respective prevalences for correct, acceptable and poor technique were 31%, 41% and 31%. Moreover, no significant difference was noted between the first and second 20-year evaluation periods.

Comment: This last review is based on an analysis from colleagues in Spain and Denmark and is a touch depressing. By reviewing the published evidence on asthma inhaler technique of more than 50,000 patients over the last 40 years, they are exploring whether we have made any progress. This article has many methodological weaknesses, including the exclusion of about 70% of studies because of missing information. It is not certain if demonstration, repeated tuition, video instruction and written materials are insufficient or just not generally implemented. Bottom line: incorrect inhaler use is unacceptably frequent and has not improved over the last 40 years.