Asthma 2015: The Year in Review

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Between January 1, 2015, and the end of October, there were >6,500 peer-reviewed papers listed in PubMed on asthma. Of necessity, those that have been selected for inclusion for this Year in Review represent a few that have caught the reviewer's interest, organized by themes. Not unexpectedly, some of these papers are in conflict with each other, whereas others raise more questions then they appear to answer. All in all, it has been a busy year in the asthma world and with new medications reaching the market in coming years, it is unlikely that this interest will abate. *Key words: asthma; obesity; pregnancy; aspirin; inhalers.* [Respir Care 2016;61(4):556–559. © 2016 Daedalus Enterprises]

Introduction

Although it is always a challenge to write a Year in Review paper, noting the best articles published on a specific topic, this is particularly so when considering the immense volume of research about asthma. Between January 1, 2015, and the end of October, there were >6,500 peer-reviewed papers listed in PubMed on asthma. Of necessity, those that have been selected for inclusion represent just a few of those that have caught this reviewer's interest. I have tried to organize these by themes.

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Asthma and Obesity

Although patients with obesity are more likely to have asthma, they are also more likely to be misdiagnosed as having asthma. The associations between these 2 conditions are still being defined. As an example, a regulatory peptide, *chitinase 3-like 1*, was shown to play a direct role in the Th2 response associated with asthma and also in the development of truncal obesity.[1] Obesity-associated asthma is not thought to be a distinct endotype. Children who are overweight and obese with early onset asthma tend to have poorer asthma control, with a fairly distinct pattern of symptoms, including greater dyspnea, increased use of short-acting β_2 agonists like albuterol, *less* methacholine responsiveness (ie, less bronchial hyper-responsiveness), *lower* exhaled nitric oxide, and less cough. Like obese adults, these children are also more prone to have gastroesophageal reflux symptoms.[2] It is hypothesized that overweight and obese children with asthma may falsely attribute exertional dyspnea and gastroesophageal reflux symptoms to asthma, leading to an excessive use of rescue medication.

If obesity is related to asthma, does weight loss improve asthma symptoms? This was a question posed in a ran-

domized parallel group study of 22 morbidly obese adults with a mean body mass index of 45.7 kg/m^2; 95% were women. Of these 22 subjects, 16 were entered in a behavioral weight reduction program for 3 months, and 6 were control subjects. After 3 months, the mean weight loss was 16.5 kg in the intervention group, but the control group had a mean weight gain of 0.6 kg. In the intervention weight loss group, there were significant improvements in methacholine bronchial hyper-responsiveness, asthma control, and quality of life, but these were unchanged in the control group. Physical activity levels also increased significantly in the intervention group but not in the control group.[3]

Risk Factors for Severe Asthma or Asthma Exacerbations

In 2010, it was reported that passage of smoke-free legislation in Scotland banning smoking in *any* public space was associated with a reduction in the rate of respiratory disease and asthma symptoms in patients.[4] In 2015, a study from the United States confirmed these findings. The authors evaluated the impact of comprehensive, statewide, smoke-free indoor air laws on second-hand smoke exposure, asthma prevalence, and asthma-related doctor visits. After enacting smoke-free laws, people in states with smoke-free indoor legislation had a lower level of second-hand smoke exposure, decreased odds of reporting current asthma symptoms (adjusted odds ratio 0.57), and a decreased frequency of doctor visits for severe asthma symptoms (relative risk 0.80) than did their counterparts in states with no legislation banning pubic smoking.[5] Of note, 27 states in the United States have enacted this type of legislation, whereas 14 states have no smoking restrictions at all.

There was also a discouraging set of papers suggesting that asthma education may not prevent asthma exacerbations. Bender et al[6] conducted a pragmatic trial of a computer speech recognition intervention that coached subjects, answered their questions, and followed up by telephone when medications were not refilled. Over 24 months, they evaluated adherence to inhaled corticosteroids (ICS) in 1,187 children $<$12 y old with persistent asthma and prescribed ICS. In the intent-to-treat analysis, adherence was 25.4% higher in the intervention group although still only 44.5%. However, asthma-related urgent care events did not differ between the groups despite greater adherence.

Even more concerning, a paper published in the Journal of Pediatrics[7] suggested that asthma knowledge was associated with a *greater* risk of hospital admission for asthma. This study enrolled 601 children $<$16 y old, who had been hospitalized for asthma. The mean age was 5 y, and 53% were African-American. Their caregivers completed a survey regarding asthma knowledge, asthma beliefs, medication adherence, child asthma severity, exposure to triggers, access to primary care, and financial strain. The authors then followed these children prospectively, and at the end of 1 y, 22% had been readmitted at least one time for asthma. Disturbingly, in the multivariate analysis, the caregiver's demonstration of increased asthma knowledge was associated with an increase in asthma readmission risk.[7] Not surprising was that children whose caregivers reported less than perfect adherence to daily medication use also had an increased risk.

Another study[8] looked at correlates of the risk of relapse following emergency department discharge for acute asthma in adults. All subjects were offered ICS therapy at discharge, and relapse rate was prospectively evaluated. Of 807 subjects, 58% were women, and relapse occurred in 18% within 4 weeks of emergency department discharge. Relapse was more common in women having prolonged symptoms before coming to the emergency department, those ever using oral corticosteroids, and the current use of ICS combination products with long-acting β agonists. To look at this another way, investigators assessed childhood asthma hospital discharge medication fills and the risk of subsequent readmission using a claims database of $>$31,000 children who had been hospitalized for asthma.[9] Although 55% had a prescription filled for a short-acting β_2 agonist and 57% for oral steroids, only 37% had a prescription filled that was given for an ICS. Readmission to hospital occurred in 6.3% of children by 90 days, and readmission was significantly less for those having a prescription filled for ICS, short-acting β_2 agonists, or a combination product. An additional sobering study[10] asked the question: Do patients who are cared for by sub-specialist physicians benefit from written action plans? This study evaluated asthma symptoms, hospital readmissions, and emergency department visits in those who were given written asthma plans and found no difference in any of these outcomes compared with those who did not receive an action plan.

Asthma in Pregnancy

Asthma in pregnancy was a active area of inquiry in 2015, with several papers that addressed questions about medications and their effect either on the developing fetus or on asthma risk. For several years, it has been known that acetaminophen (paracetamol) in pregnancy and early childhood is associated with a significantly increased risk of the child developing asthma. This was confirmed in 2 studies[11,12] published in 2015 that also adjusted for respiratory infections, under the assumption that if the acetaminophen was taken to treat respiratory infection and fever, then the infection itself might explain the increased risk. What these studies showed was that both mothers who took acetaminophen during early pregnancy and in-

fants who took acetaminophen were at significantly increased risk of developing asthma and that this risk was mitigated but not abolished when respiratory tract infections were accounted for.[11,12] The teratogenicity risk of asthma medications to the developing fetus was addressed in 2 studies. The EXPECT study[13] evaluated the risk of omalizumab (Xolair) in pregnancy, evaluating 191 pregnant women who were exposed to omalizumab during their first trimester. Of the 168 pregnancies with known outcomes and a median exposure during pregnancy of 8.8 months, 160 infants were born, including 4 twin pairs. The proportion of major congenital abnormalities, prematurity, low birthweight, and small size for gestational age observed in those women who received omalizumab during pregnancy was similar to that of women with asthma who did not receive omalizumab, suggesting that there is no apparent increased prevalence of major abnormalities associated with receiving omalizumab during pregnancy. The risk of congenital malformations was also evaluated[14] in pregnant women using either high-dose ICS or long-acting β agonist + ICS combination therapy. In this cohort of women exposed during the first trimester over a 10-y period, there was no increased risk of major malformations in the long-acting β agonist + ICS combination or in the ICS therapy at higher doses, confirming that both medications should be considered relatively safe during pregnancy. An excellent review of asthma management in pregnancy was also published in 2015.[15]

Asthma-COPD Overlap Syndrome

I have heard it said that the world can be divided into lumpers and splitters. The relationship between asthma and COPD has been defined for many years by the Dutch hypothesis (lumpers) that notes that young people with asthma who later take up smoking are far more likely to develop COPD, that COPD begins in early childhood with infections, and asthma is part of the COPD continuum. The British hypothesis (splitters) was that asthma is an allergic Th2 response that is more commonly seen in young children and the elderly, whereas COPD consists of bronchitis and emphysema, predominantly as a result of smoking tobacco. In recent years, the splitters have been gaining ground, with phenotyping (more correctly, endotyping) asthma being the scientific flavor of the day. In the last 2 years, an emphasis has been on an endotype called the asthma-COPD overlap syndrome. Asthma-COPD overlap syndrome might be described as occurring in smokers who have chronic expiratory airway obstruction despite treatment and features of both asthma and COPD, or patients with asthma who smoke and have fixed air-flow obstruction. At least 2 studies[16,17] have used cluster analysis to identify asthma-COPD overlap syndrome, and despite the unique features of this syndrome, most asthma-COPD overlap syndrome sufferers respond to therapy with ICS, and there is no evidence for using specifically targeted therapy, paradoxically supporting both the Dutch and British hypotheses.[18] However, a study[19] evaluating acute respiratory events comparing COPD with asthma-COPD overlap syndrome suggested that the prevalence of asthma-COPD overlap syndrome increases with age, the overall prevalence is about 17.4% of a cohort of 17,088 COPD subjects, and there is a greater incidence of acute respiratory events (exacerbations) in the asthma-COPD overlap syndrome group compared with COPD alone (11.5 vs 4.62/100 patient y).

Miscellaneous

Asthma also occurs in elite athletes, and these athletes appear to have similar bronchial hyper-responsiveness and symptoms compared with patients with atopic asthma who are not competitive athletes. However, the elite athletes with asthma did not have predominant signs of atopy. It is probably not surprising that elite winter athletes have more exercise-related symptoms than competitive swimmers with asthma.[20]

The United States is one of only 2 countries in the world that allows direct-to-consumer advertising of prescription drugs. An ecological study,[21] conducted from 2005 to 2009, evaluated the impact of direct-to-consumer advertising using data from television ratings and insurance data regarding the volume of total new and refilled prescriptions, prescription claims, hospitalizations, and out-patient encounters for asthma. These data were evaluated for 75 market areas in the United States, looking at the role of direct-to-consumer advertising for Advair, Asmanex, Singulair, and Symbicort (4 of the most heavily promoted asthma medications during this time period). After adjustment, each additional television advertisement was associated with a 2% higher pharmacy sales rate over the 5 y. However, among those commercially insured, direct-to-consumer advertising was significantly associated with an *increased* number of emergency department visits related to asthma but no increase in the number of hospitalizations.

Some adults with asthma are sensitive to acetylsalicylic acid (aspirin) and other salicylate compounds. Many of these patients have so-called triad asthma, with chronic asthma and sinusitis, aspirin sensitivity, and nasal polyps. A systematic review and meta-analysis[22] was conducted to determine the prevalence of aspirin-exacerbated respiratory disease in adults with asthma, identifying 27 published studies considered appropriate for inclusion. Prevalence rates of aspirin-exacerbated respiratory disease ranged from 5.5 to 12.4% among subjects with known asthma, with a median of 7% in adult subjects with mild to moderate asthma and twice that percentage in subjects

with severe asthma. The authors concluded that early identification of aspirin-exacerbated respiratory disease is important because there is increased morbidity and cost associated with asthma exacerbations in patients unaware of aspirin sensitivity. Patients with aspirin-exacerbated respiratory disease can safely receive aspirin treatment after desensitization.

Also, of special interest to respiratory therapists, a study[23] was published evaluating the impact of enforcing the Montreal protocol banning chlorofluorocarbon albuterol metered-dose inhalers. On December 31, 2008, chlorofluorocarbon inhalers were banned and replaced by more expensive branded hydrofluoroalkane inhalers. Using insurance data over a period of 7 y, the authors found that albuterol costs rose in 2004 from $13.60 per canister to $25 immediately after the 2008 ban, but by 2010, the price had decreased to $21 per canister. There was a steady decrease in albuterol inhaler use from 2004 to 2010, with a steep decline in generic chlorofluorocarbon inhaler use starting in the fourth quarter of 2006, offset by an increase in hydrofluoroalkane inhalers. They also found that a $10 increase in out-of-pocket albuterol prescription costs decreased utilization by just under 1% for adults and by 0.5% for children, but this did not appear to affect asthma-related hospitalizations, emergency department visits, or outpatient visits.[23]

Of the more than 6,500 papers related to clinical aspects of asthma and published between January and October 2015, a selection of them are reviewed. These highlight trends in asthma research, care, and epidemiology. All in all, it has been a busy year in the asthma world, and with new medications reaching the market in coming years, it is unlikely that this interest will abate.

REFERENCES

1. Ahangari F, Sood A, Ma B, Takyar S, Schuyler M, Qualls C, et al. Chitinase 3-like-1 regulates both visceral fat accumulation and asthma-like Th2 inflammation. Am J Respir Crit Care Med 2015;191(7):746-757.
2. Lang JE, Hossain MJ, Lima JJ. Overweight children report qualitatively distinct asthma symptoms: analysis of validated symptom measures. J Allergy Clin Immunol 2015;135(4):886-893.e3.
3. Pakhale S, Baron J, Dent R, Vandemheen K, Aaron SD. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma? Chest 2015;147(6):1582-1590.
4. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. N Engl J Med 2010;363(12):1139-1145.
5. Lin HC, Park JY, Seo DC. Comprehensive US statewide smoke-free indoor air legislation and secondhand smoke exposure, asthma prevalence, and related doctor visits: 2007-2011. Am J Public Health 2015;105(8):1617-1622.
6. Bender BG, Cvietusa PJ, Goodrich GK, Lowe R, Nuanes HA, Rand C, Shetterly S, Tacinas C, Vollmer WM, Wagner N, Wamboldt FS, Xu S, Magid DJ. Pragmatic trial of health care technologies to improve adherence to pediatric asthma treatment: a randomized clinical trial. JAMA Pediatr 2015;169(4):317-323.
7. Auger KA, Kahn RS, Davis MM, Simmons JM. Pediatric asthma readmission: asthma knowledge is not enough? J Pediatr 2015;166(1):101-108.
8. Rowe BH, Villa-Roel C, Majumdar SR, Abu-Laban RB, Aaron SD, Stiell IG, et al. Rates and correlates of relapse following ED discharge for acute asthma: a Canadian 20-site prospective cohort study. Chest 2015;147(1):140-149.
9. Kenyon CC, Rubin DM, Zorc JJ, Mohamad Z, Faerber JA, Feudtner C. Childhood asthma hospital discharge medication fills and risk of subsequent readmission. J Pediatr 2015;166(5):1121-1127.
10. Sheares BJ, Mellins RB, Dimango E, Serebrisky D, Zhang Y, Bye MR, Dovey ME, Nachman S, Hutchinson V, Evans D. Do patients of subspecialist physicians benefit from written asthma action plans? Am J Respir Crit Care Med 2015;191(12):1374-1383.
11. Cheelo M, Lodge CJ, Dharmage SC, Simpson JA, Matheson M, Heinrich J, Lowe AJ. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. Arch Dis Child 2015;100(1):81-89.
12. Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA Jr, et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. J Allergy Clin Immunol 2015;135(2):441-448.
13. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr., Chen H, Carrigan G, et al. The Xolair pregnancy registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol 2015;135(2):407-412.
14. Eltonsy S, Forget A, Beauchesne MF, Blais L. Risk of congenital malformations for asthmatic pregnant women using a long acting beta agonist and inhaled corticosteroid combination versus higher-dose inhaled corticosteroid monotherapy. J Allergy Clin Immunol 2015;135(1):123-130.
15. Kelly W, Massoumi A, Lazarus A. Asthma in pregnancy: Physiology, diagnosis, and management. Postgrad Med 2015;127(4):349-358.
16. Reddel HK. Treatment of overlapping asthma-chronic obstructive pulmonary disease: can guidelines contribute in an evidence-free zone? J Allergy Clin Immunol 2015;136(3):546-552.
17. Fingleton J, Travers J, Williams M, Charles T, Bowles D, Strik R, et al. Treatment responsiveness of phenotypes of symptomatic airways obstruction in adults. J Allergy Clin Immunol 2015;136(3):601-609.
18. Ghebre MA, Bafadhel M, Desai D, Cohen SE, Newbold P, Rapley L, et al. Biological clustering supports both "Dutch" and "British" hypotheses of asthma and chronic obstructive pulmonary disease. J Allergy Clin Immunol 2015;135(1):63-72.
19. Chung WS, Lin CL, Kao CH. Comparison of acute respiratory events between asthma-COPD overlap syndrome and COPD patients: a population-based cohort study. Medicine 2015;94(17):e755.
20. Boulet LP, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. N Engl J Med 2015;372(7):641-648.
21. Daubresse M, Hutfless S, Kim Y, Kornfield R, Qato DM, Huang J, Miller K, Emery SL, Alexander GC. Effect of direct-to-consumer advertising on asthma medication sales and healthcare use. Am J Respir Crit Care Med 2015;192(1):40-46.
22. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. J Allergy Clin Immunol 2015;135(3):676-681.e1.
23. Jena AB, Ho O, Goldman DP, Karaca-Mandic P. The impact of the US Food and Drug Administration chlorofluorocarbon ban on out-of-pocket costs and use of albuterol inhalers among individuals with asthma. JAMA Intern Med 2015;175(7):1171-1179.