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Review

2012–2013 – The Year in Preview

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SUMMARY

A highlight of many journals is a review of pertinent literature in a specific field that has been published in the preceding year. Although such "Year in Review" presentations are important, at PRR we are pleased to present the news that has not yet happened. In this manuscript, which is a combination of science and fiction, I will present the very best research that has not yet been conducted but will be published sometime in 2012 or 2013. This will cover all aspects of paediatric pulmonary disease. Any resemblance to real research that is actually published during this time period is strictly coincidental and the product of a fertile imagination. However, if these ideas inspire you to do these studies and publish the results it would make this science fiction even more interesting. To quote the famous baseball player, Yogi Berra, "It's difficult to make predictions, especially about the future."[1]

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INTRODUCTION

With the laudable objective of bridging the gap between science and imagination as previously championed by Nostradamus, the plausible preliminary results of cutting edge research in paediatric respiratory medicine are presented.

Asthma medications

Although studies have shown that there is no therapeutic role for beta agonists in the treatment of bronchiolitis,[2] it is still common practice to prescribe these medications when there is persistent wheezing in infants following a viral illness. A study conducted in two large paediatric practices, similar in size and population demographics and located in the US Midwest, suggested that daily salbutamol use in the first year of life might increase the risk and severity of asthma at age 7. In this study, one of these practices routinely placed well children with documented bronchiolitis on twice daily nebulized salbutamol for a full year while the other practice did not use salbutamol during or after the diagnosis of bronchiolitis in that first year. A total of 633 children were enrolled and 557 were followed until age 7. The subjects were similar in age of diagnosis, the gender, atopy as defined by medical history and the presence of eczema, social economic status, and race. They were evaluated by both pulmonary functions and asthma questionnaire. The prevalence of asthma was 36% greater in those infants who received salbutamol for one year even after correcting for confounding variables. The authors speculate that the early use of salbutamol could alter the immune response to allergens, the expression of beta receptors in the airway, or the growth of airway smooth muscle.

Animals that are sensitized and develop asthmatic inflammation have decreased inflammatory cytokines and eosinophils in bronchial lavage fluid after receiving beta-blockers.[3] In a clinical study, adults with very severe asthma enrolled in the NIH Severe Asthma Research Program were given a beta-blocker or placebo for 28 days. Of the subjects taking the beta-blocker, 22 of 58 were able to safely decrease or discontinue oral steroids as opposed to only 12 of 54 given placebo. Subjects taking the beta-blocker had a 38% decrease in inhaled nitric oxide. Only five had increased symptoms that were attributable to the beta-blocker.

Airway mucus, cilia and smooth muscle in asthma

Patients who die of asthma have airways filled with secretions and people with middle lobe syndrome have excessive secretions and an asthma type condition.[4] Genome wide association studies suggested that secretory phospholipases A2 (sPLA2) appears to be responsible for some forms of plastic bronchitis; especially in sickle cell acute chest syndrome where elevated sPLA2 is a marker for exacerbations.[5] Increased sPLA2 was also identified in the bronchial lavage of persons with middle lobe syndrome and in the airway of persons who died of asthma. Increased sPLA2 was associated with steroid resistance, mucus hypersecretion and secretory hyperresponsiveness.

Following the discovery of taste receptors on airway epithelial smooth muscles by Liggett and colleagues at the University of Maryland and the observation that bitter tastants produce greater

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bronchodilatation than a beta agonist,[6] investigators at the Monel Institute in Philadelphia report that the ciliated epithelium of the airway responds to odours and there are olfactory receptors on these cilia. The olfactory epithelium in the nose is a non-motile ciliated epithelium and it had always been assumed that motile cilia did not respond to smells. The presence of olfactory receptors in response to different smells suggests that motile cilia in these receptors may play a role in the airway's response to nasal irritants and odours and may explain such phenomena as perfume induced asthma. This may also introduce new possibilities for aromatherapy for diseases of the airway.

Airway smooth muscle in persons with severe asthma is resistant to apoptosis[7] due to deficiency in caspase 3 caused by down regulation of casp3G. Not only is there smooth muscle hypertrophy, but apoptosis resistance lead to airway smooth muscle hyperplasia. However, the caspase-independent apoptotic pathway is preserved and if it is activated in asthmatic mice it shrinks hypertrophied airway smooth muscle. This was called "molecular thermoplasty" by these investigators.

Infections and asthma

Human rhinovirus C triggers most asthma attacks in children and causes more severe attacks than other rhinoviruses or other viruses.[8] The human rhinovirus C genome was sequenced and reverse engineered.[9] Using these data, investigators developed a rhinovirus vaccine that they are calling AsthmaVax®. This Human rhinovirus C immunization was safe in long-term animal studies and in Phase 1 clinical trials. Further clinical trials for prevention of asthma and exacerbations in patients who are susceptible to frequent exacerbations will start in late 2013.

Even the healthy airway has now been shown to contain low numbers of bacterial flora; the airway microbiome. This complex community of bacteria may contribute to clinical features of asthma as the airway microbiome is a modulator of glucocorticosteroid receptor activity and colonization by specific bacteria may contribute to persistence of inflammation, disease presentation, and/or disease heterogeneity. The NHLBI's Asthma Clinical Research Network, reported that using a microarray-based method that detects distinct 16S rRNA gene sequences, taxa in the phylum *Proteobacteria* were the most abundant in bronchial brushings were from 65 asthma subjects and 10 healthy subjects and that asthmatic subjects had significantly greater bacterial diversity than controls. Furthermore, the subjects with asthma who had the highest bacterial diversity and received low dose clarithromycin treatment had the greatest improvement in airway hyperresponsiveness following treatment.[10] Additional research suggests that the newborn-mother dyad have a unique shared microbiome and that infants born to a mother with asthma and who developed multi-trigger wheezing after age 3 years have a specific skin (umbilical) microbiome within hours of birth that is homologous to the vaginal microbiome during the 2nd trimester. Furthermore, a specific set of anaerobic bacteria identified on both maternal vaginal and neonatal skin sampling is strongly predictive of both asthma and corticosteroid responsiveness.

Inflammation, epigenetics, and asthma

Heritable epigenetic changes in DNA can be passed from smoking mothers to children and even from grandmothers.[11] This "third hand" smoking inhibits histone deacetylase 2 in airway antigen presenting cells enhancing the development of the Th2 program. Histone deacetylase inhibition is synergistic with atopic mediator exposure and appears to promote the asthmatic response by inducing a Th2 response in susceptible individuals.

Environmental oil spills produce massive toxic contamination and have been associated with many health problems in those exposed; including an increased risk and severity of airway diseases.[12] It has now been demonstrated that asthma exacerbations are greater in subjects living along the area affected by the Gulf Coast oil spill. Subjects living along the coast of Louisiana and Mississippi who had the heaviest exposure to the Gulf oil spill through clean up efforts, recreational activities, or job occupation had nearly a three fold increase in exacerbations of asthma compared to similar subjects with asthma living in the same the area who did not have these exposures. A similar, but smaller, increase in asthma was reported in the children of those exposed. This increase was directly related to the intensity of exposure and was thought either to be due to the effects on the immune system, effects of stress, or volatile respirable compounds released as part of the spill.

Based on data showing a decreased risk of asthma in susceptible children exposed to barnyard dust in infancy,[13] a company in Munich Germany has developed and is selling an odour free composter and barn dust dispersal device; the Ramstall®. Meant for use in urban homes, it provides constant exposure to activated barn dust particulates while it composts kitchen waste and helps to prevent asthma in susceptible families.

Vitamin D, obesity, and asthma

Vitamin D increases steroid responsiveness in asthma by up regulating the airway glucocorticoid receptor and glucocorticosteroid insensitivity in asthma is strongy associated with vitamin D deficiency.[14] An aerosol form of 25-hydroxy Vitamin D was shown to be safe in experimental animals and produced high concentrations of active vitamin D that persisted for at least 24 hours in the airway. Two weeks of aerosol vitamin D significantly decreased airway hyperresponsiveness in animals with experimental asthma. Initial clinical trials are planned for late 2013.

Vitamin D deficiency, defined as concentrations of less than 20 ng/mL of 25-OH Vitamin D, is common in pregnant women, especially in the inner city.[15] Maternal and neonatal vitamin D deficiently is also associated with a 2.3 (maternal) and 4.1 (neonatal) fold increase in childhood asthma by age 6 ($p < 0.001$). In November 2012 the American College of Obstetrics and Gynecology published new guidelines for perinatal care that recommended vitamin D supplementation for all pregnant women.

Both the prevalence of asthma and obesity are increasing and it has been shown that the risk of asthma significantly increases with increasing body-mass index.[16] It has also been shown that profound weight loss can improve asthma control in morbidly obese patients.[17]

A study was conducted in 56 non-smoking adults over the age of 16, who had physician diagnosed asthma and morbid obesity defined as a body-mass index greater than 40 kg/m^2. Half were assigned to a strict weight loss diet and monitored exercise and the remainder underwent gastric bypass surgery and exercise rehabilitation. After six months those in the gastric bypass group lost a mean on 68% of their body mass compared with a 6% sustained loss in the diet group. There was no change in asthma severity in the diet group while for those receiving gastric bypass surgery, the severity of asthma and frequency of exacerbations decreased dramatically and this was strongly correlated with the decrease in body mass index.

Genetics and sleep deprivation

Although it has been shown that persistent sleep apnoea and hypoxemia is associated with metabolic, inflammatory, and

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