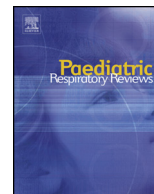




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Review

Asthma myths, controversies, and dogma

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EDUCATIONAL AIMS THE READER WILL BE ABLE TO:

- Understand the importance of a detailed history when considering a diagnosis or erroneous diagnosis of asthma in children.
- Appreciate that “exercise induced asthma [EIA]” is a term overused when describing children with dyspnea related to deconditioning, obesity and anxiety.
- Recognize that most children with chronic cough and no other symptoms, rarely have asthma as the cause of their cough
- Know that although obesity increases the risk of concomitant asthma, that it is also true that obese children and adults with dyspnea are often misdiagnosed as having asthma.
- Share their understanding of the difference between evidence and myth in the management of childhood asthma.

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SUMMARY

Although the symptom complex we call asthma has been well described since antiquity, our understanding of the causes and therapy of asthma has evolved. Even with this evolution in our understanding, there are persistent myths (widely held but false beliefs) and dogma (entrenched beliefs) regarding the causes, classification, and therapy of asthma.

It is sobering that some of the knowledge we hold dear today, will become the mythology of tomorrow.
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INTRODUCTION

Asthma is a disease known since antiquity, with one of the first descriptions by Aretaeus of Cappadocia [1]. Maimonides suggested “the soup from a fat hen” as a useful therapy in his *Treatise on Asthma* [2]. Asthma is now generally defined as recurrent and (somewhat) reversible airflow obstruction due airway inflammation, smooth muscle bronchospasm, and mucus hypersecretion [3]. Given the role of inflammation in asthma, and the groundbreaking work by Steve Rennard and his wife, demonstrating that traditional home-made chicken soup has anti-inflammatory properties *in vitro* [4], Maimonides' earlier work shows significant insight. Over the years, there have been many beliefs about asthma. Some of these have been proven to be incomplete or incorrect. Some of these myths are more pervasive among patients; others exist as controversies among physicians and scientists. The aim of this paper is to look at a few of these myths,

mistakes, controversies, and dogma with the realization that some of the things that we currently believe will be fodder for laughter and scorn in a few years.

EPIDEMIOLOGY AND DEFINITIONS

The definition and epidemiology of asthma is an area that has been rife with controversy with the British, Dutch, and others weighing in over the years [5]. In 1980, Nick Gross famously asked, “What is this thing called love?” with regards to defining asthma [6]. The answer from Prof Gross was that we all know what love (asthma) is but are not always willing to accept another's definition. This is very similar to the definition of pornography by the US Supreme Court Justice Potter Stewart who in 1964 suggested that a precise definition was not possible but, “I know it when I see it” [7]. Let's move on from pornography to something much more controversial – the definition and epidemiology of asthma.

Asthma is an infectious disease

In the 1950's and early 1960's asthma was considered to be due to chronic bacterial infection and it was proposed that antibiotics

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would be effective therapy [8]. Although no specific bacterial pathogens were isolated from the airways of patients with asthma, the practice of using antibiotics led to the unexpected discovery that the macrolide antibiotics had immunomodulatory properties quite separate from antimicrobial properties [9]. A decade ago, it was believed that many patients with severe asthma were chronically infected with *Mycoplasma* or *Chlamydia*, and there was a suspicion that this might be part of the mechanism of action for macrolide antibiotics in asthma therapy [10]. However, trials of macrolide therapy in adults with poorly controlled asthma have shown clinical benefit unrelated to infection with these organisms [11].

There are now data showing that infection does play a role, probably a key role, in asthma. There appears to be an increased susceptibility to human rhinovirus in persons with asthma [12] and human rhinovirus infection is the most frequently reported cause of acute severe exacerbations of this disease [13]. The role of RSV in asthma predisposition is far more controversial. A prospective study was conducted in 27 centers to examine the effect of palivizumab on recurrent wheeze in infants <36 weeks gestation with and without a family history of atopy in infants who did (N=146) or did not (N=171) receive palivizumab. There was no effect of palivizumab on recurrent wheezing in the 90 children with a family history of atopy compared to 130 untreated infants with atopic families suggesting that RSV perhaps predisposes to wheezing in an atopy-independent mechanism [14].

Even more interesting is work on the airway microbiome in health and disease. The airways below the larynx were once thought to be sterile in healthy persons, but it is now known that there is a resident microbial population in all airways – the microbiome. Early studies indicate that loss of diversity in this microbiome and predominance of pathogens such as *Haemophilus*, may characterize the airway microbiome of patients with asthma [15]. It is not clear to what extent these changes are due to the disease itself or to the therapy (e.g. inhaled corticosteroids).

We may be coming around to asthma being an infectious disease after all.

Asthma is an allergic disease

Over half of children with asthma also have allergies, both allergies and asthma are associated with a TH2 inflammatory response, and allergens are known to trigger acute asthma. However many patients with asthma do not have allergies, including most with adult onset asthma [16]. Thus while it is clear that allergy is one of the co-morbidities associated with asthma and that treatment of allergy or allergen avoidance may decrease the severity of asthma, it is probably incorrect to state that asthma is an allergic disease.

Asthma is a bronchospastic disease

Airway smooth muscle hypertrophy and bronchospasm is a characteristic of asthma, however it is inappropriate to refer to asthma as “reactive airways disease” or as “bronchospasm”. This abhorrent nomenclature has come about for several reasons. As to bronchospasm; bronchodilator medications are readily available and extremely effective at relieving acute asthma, the evaluation and diagnosis of asthma often hinges on the demonstration of bronchial hyperresponsiveness to bronchoprovocation challenge or to the reversal of airflow limitation when patients inhale a bronchodilator in the pulmonary function laboratory. However, it is possible to have airway hyperresponsiveness to provocation testing without having signs or symptoms of asthma [17]. So while there is bronchospasm, particularly in acute asthma, asthma cannot be and should not be defined as a bronchospastic disease.

As for the rationale for using the term, “reactive airways disease”; I am well aware that there is no cure for “stupid” [18].

Children outgrow asthma

This is a belief sometimes held by general practitioners and by many parents. As airways grow, and particularly as boys approach adolescence and airway diameter increases, asthma symptoms can abate [19]. However patients with moderate or severe asthma rarely have resolution of their symptoms even with good adherence to controller therapy [20]. It is better that we think of asthma as a lifelong illness that can be well controlled, than as merely a phase of childhood. Children requiring daily therapy for asthma certainly outgrow their paediatrician, but probably not their asthma.

There is an asthma epidemic

By reading the newspaper (does anyone still read newspapers?) or the Internet, it is easy to get the impression that there are epidemics of many diseases these days; gluten enteropathy, attention deficit hyperactivity disorder, and asthma to name but a few. In a subspecialty practice of pediatric pulmonary, one is just as likely to encounter the over diagnosis of asthma as the under diagnosis [21]. I believe that this is because patients with true asthma who are adherent to their controller therapy usually do well and so are rarely referred to a subspecialty practice. It is those who are not taking their medication appropriately or do not have asthma at all that we see in our practice. It is likely that asthma is both under and over diagnosed but there are no clear epidemiologic data supporting an “epidemic”. In many countries, death from asthma has been declining over the past two decades due in part, to better recognition and better therapy [22].

Studies show that about 30% of adults with physician-diagnosed asthma have been misdiagnosed and that incorrect diagnosis is more common in children and the elderly [23]. Asthma misdiagnosis is also more common in obese adults, especially men, who use the resources of emergency departments frequently for treatment of dyspnea [24]. At the other end of the spectrum, asthma is quite uncommon before the age of 2 years [25] and yet many children with intermittent viral induced wheezing are treated with corticosteroids and incorrectly carry a diagnosis of asthma (or reactive airways disease).

Chronic cough usually means asthma

Many children with asthma also cough, and although there is a phenotype of asthma, referred to as cough variant asthma or cough dominant asthma (my preferred term), this seems to be associated with airway mucus hypersecretion and poor response to beta agonist bronchodilators [26]. However, chronic cough as a sole symptom of childhood asthma is rare, representing less than 4% of those children with cough that persists for more than 3 weeks [27].

Dyspnea with exercise is usually due to asthma

Poorly controlled asthma can lead to shortness of breath with exercise. However, it has been my observation that the diagnosis of “exercise induced asthma” (EIA) is more commonly made in high performing athletes who have dyspnea when pushing to excel and that these young athletes almost never have true asthma when exercise testing is performed appropriately. These patients are often placed on a short-acting bronchodilator before exercise or even inhaled corticosteroids (ICS) without appropriate testing.

Sear and colleagues studied 52 children referred for investigation of poorly controlled EIA but only 8 (15.4%) fulfilled the diagnostic criteria for EIA defined as a 10% or greater decrease in FEV1 with exercise. 23.1% were unfit, 26.9% had vocal cord dysfunction, 13.5% had a habit cough, and 21.1% had no

abnormalities on clinical or laboratory testing [28]. The initial reported symptoms of wheeze or cough often changed following a careful history, particularly among the elite athletes. These results are consistent with studies performed by Weinberger and colleagues demonstrating that when children or adolescents with dyspnoea on exercise have cardiopulmonary exercise testing, most have physiologic limitation of exercise, with very few having true EIA [29].

This myth has also been associated with another; that children with asthma should not exercise. This is rubbish. One of the main goals of asthma therapy is to control symptoms well enough that the patient can exercise without difficulty related to asthma. Asthma symptoms are bad. Exercise is good.

ALLERGY AND ASTHMA

Allergy immunotherapy is effective for treating asthma

Allergy immunotherapy, given by injection or by sublingual administration, appears to be effective at reducing the allergic response to specific allergens and immunotherapy is beneficial in many patients for the treatment of classic hay fever. The data regarding the benefits of immunotherapy for the treatment of asthma is less robust with low grade evidence of effectiveness in reducing symptoms or preventing disease [30]. However multifaceted interventions to reduce inhalant and food allergen exposure appears to decrease asthma diagnoses in susceptible toddlers and young children [31]. Therefore, it is prudent to explain that immunotherapy can be effective for patients with inadequately controlled allergy, but is far less effective for the treatment of asthma. It is likely that regular therapy for persistent asthma will still be required despite immunotherapy.

Moving to a dry climate will improve asthma

Patients with asthma are sometimes told that if they moved to a hot and dry climate, they would have fewer symptoms. Paradoxically others are told that moving to a coastal city will reduce symptoms. While it is true that in very dry climates there are fewer molds, and very hot climates, such as the desert tend to have fewer trees that produce pollen, often these areas come with their own set of allergens. The paradox is that some urban centers in the desert, such as Phoenix in the United States, have become lush with greenery because the people moving to these climates from more humid environments miss having green lawn and flowering plants around and irrigate heavily to support this plant life.

People with asthma should not have pets. Corollary: Certain breeds of dogs are hypoallergenic.

It is possible to develop allergies to foreign proteins in the dander (hair and skin) of almost any hairy or furry pet. Provocative data, consistent with the “hygiene hypothesis”, suggest that having a dog (but not a cat) in the home at the time a child is born will reduce the risk of asthma and allergy in later life [32], while acquisition of a dog after a year of age does not have the same protective effect. This is probably due to changes in the gut microbiome associated with early childhood exposure to potential allergens [33].

It has also been said that certain breeds of dog are less allergenic than others. A persistent myth in Latin America is that if you have a child with asthma and acquire a Chihuahua dog, the child will be cured because the asthma symptoms are transferred to the dog. While there are fur dogs, such as poodles that do not shed, and hair dogs that shed their coat, it does not appear that any breed of dog is less “allergenic” than any other [34].

DRUGS AND THERAPY

The long-term use of ICS is disease modifying

It is an attractive hypothesis that ICS will block asthmatic airway inflammation and thus can decrease the long-term severity of asthma or airway remodeling. Although ICS are the most effective medications to treat asthma, there are no data that long-term use is disease modifying.

The early use of inhaled fluticasone propionate for wheezing in preschool children has no effect on the natural history of asthma or wheeze later in childhood, and does not prevent lung function decline or reduce airway reactivity [35]. In a large study of preschool children at high risk for asthma, two years of ICS therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year [36]. The early use of ICS may also carry some risk of impairing lung growth and development. Infant rhesus monkeys with “asthma” who were given ICS had disruption of postnatal lung growth and differentiation of airways and lung parenchyma [37]. Thus it is safe to say that use of ICS can decrease the symptoms of asthma but are not disease modifying.

ICS are addictive

This is not a myth that is held by many physicians, but some patients and families are concerned that the long term use of ICS will decrease the response to medication or make the body “dependent” on receiving ICS. These misconceptions may come from accurate reports in the lay press that unrestricted antibiotic use can lead to the development of drug resistance in bacteria; while addiction to medications such as barbiturates and opioids are also commonly knowledge. It is important to recognize that our patients may not recognize that asthma therapy is different and thus, part of asthma education is anticipating this misunderstanding.

Medications delivered by jet nebulizer work better and more quickly than those given by pressurized metered dose inhaler (pMDI) to treat acute or severe asthma

I have written extensively about this myth [38–40]. When used appropriately, there is no difference between the effectiveness of a bronchodilator medication administered by nebulization when compared to the same medication given by pMDI [41]. The difference is that patients receive much larger doses by nebulization, are more likely to have greater systemic effects, and adherence to nebulized medication administration is worse [42].

Levalbuterol (levosalbutamol) is safer and more effective than racemic salbutamol

Levalbuterol or levosalbutamol is the *R*-enantiomer of the short-acting β_2 -adrenergic receptor agonist, salbutamol. The development of the single isomer salbutamol was driven by knowledge of receptor pharmacology as the *R*-enantiomer produces bronchodilation while the *S*-enantiomer does not. In humans, there is more than 100 fold greater binding of the bronchodilator *R*-enantiomer to the beta receptor with almost no binding of the ineffective *S*-enantiomer [43]. Studies confirm that the benefits and side effects of levosalbutamol are identical to those of racemic salbutamol; except that levosalbutamol is usually more expensive [44]. The lack of difference in reported side effects is even true in children with cardiac disease given racemic or levosalbutamol [45]. In one study of very severe, acute asthma in children, racemic salbutamol was superior to levosalbutamol with

respect to changes in FEV1 and asthma score, when each was administered as continuous nebulization. There was no significant difference between the drugs with respect to admission rates or side effects [46].

Beta agonists improve mucus clearance

Beta agonists can increase ciliary beat frequency *in vivo* but mucus clearance is dependent not only on ciliary beat frequency, but also on power, the integrity of the epithelium, and the properties of mucus. In some species, beta agonists are mucus secretagogues [47]. Well conducted studies by Anderson and Daviskis have shown that inhaled beta agonists do not increase mucociliary clearance in persons with chronic severe asthma [48].

Salbutamol must be given frequently and in high dosage during an acute asthma exacerbation

Frequent and high dose short acting beta agonists are a mainstay of therapy for acute severe asthma, yet frequent and high dosage also carries risks decreasing beta receptor expression, hypokalemia, hyperglycemia, abnormal cardiac rhythm, tremor and anxiety. Furthermore, high dose continuous beta agonist therapy confers no benefits over usual intermittent aerosol therapy in adults [49] or in children [50]. Patients dying of asthma in my hospital rarely die from beta agonist deficiency. I suspect that physicians give more beta agonist than needed to produce optimal bronchodilatation and that this can contribute to morbidity. It will be up to investigators with courage to test this in a randomized clinical trial.

Asthma phenotypes are stable though out life. Corollary: asthma severity is intrinsic to the patient and needs only to be categorized at initial presentation.

This is a carry-over from earlier guidelines that suggested that asthma severity should be evaluated at first diagnosis and that “label” would remain with the patient forever. Since our long term goal is to decrease severity by optimizing control, it doesn't make sense that severity should be classified only at diagnosis. Therefore, asthma severity scoring is now based on symptoms after achieving maximal control with medication [3]. In a similar fashion, there is a passion for phenotyping or endotyping asthma, but it is likely that these phenotypes are non-static and can change with time and growth, co-morbidities, therapy, and environmental exposures.

CONCLUSION

Although this concludes our brief (and undoubtedly, partial) exploration into myths and dogma related to childhood asthma, it does not end our opportunities either to deflate these myths or, unfortunately, our vast abilities to create new myths and dogma. Albert Einstein is quoted as saying, “Only two things are infinite, the universe and human stupidity, and I'm not sure about the former” [51].

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