

New visions in respiratory allergy (asthma and allergic rhinitis): An iPAC summary and future trends

Papadopoulos NG, Borres M, Gern J, Nieto A. New visions in respiratory allergy (asthma and allergic rhinitis): An iPAC summary and future trends.

Pediatr Allergy Immunol 2008; 19 (Suppl. 19): 51–59.

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In many aspects, respiratory allergies, i.e., allergic asthma and rhinitis, represent the hallmarks of allergy. Epidemiologic data highlight their large prevalence of most parts of the world, socioeconomic analysis reveal their large impact on global health and the large number of scientific publications in this field regularly brings to light many new aspects of these diseases. However, the current understanding of respiratory allergies, in particular in children remains scarce. How can we efficiently prevent respiratory allergies in allergy-prone infants? How can we prevent the progression of the disease? What therapeutic strategies could efficiently address efficient immunomodulation? The international Pediatric Allergy and Asthma Consortium, addressed these issues by a thorough review of the literature providing a state-of-the-art current knowledge in respiratory allergy, and identified a series of needs to be addressed in future studies.

Nikolaos G. Papadopoulos¹, Magnus Borres², James Gern³ and Antonio Nieto⁴

¹Department of Allergy, 2nd Pediatric Clinic, University of Athens, Athens, Greece, ²Phadia AB, Uppsala, Sweden, ³Department of Pediatrics, University of Wisconsin Medical School, Madison, WI, USA, ⁴Pediatric Allergy Unit, Children's Hospital La Fe, Valencia, Spain

Key words: asthma; wheeze; rhinitis; children; environment

Nikolaos G. Papadopoulos, Allergy Research Center, 41, Fidippidou, 11527, Goudi, Greece
Tel.: +30 210 777 6964
fax: +30 210 777 7693
E-mail: ngp@allergy.gr

Conflict of interest: N.G.P. has received grant support and/Dr consultation fees from AstraZeneca, GSK, MSD, Novartis, Schering Plough and UCB; M.B. is employed by Phadia AB; J.G. has acted as a paid consultant for Merck Inc. and GSK and is the PI of an investigator-initiated clinical research project sponsored by Merck Inc.; A.N. declares no conflict of interest.

Accepted 11 February 2008

Asthma and allergic rhinitis are the most frequent allergic diseases and, judging by numbers of publications and other objective markers, among the 'hottest' topics in current medicine. The considerable overlap of these two conditions, both in terms of morbidity and mechanisms, has been driving a trend to consider them as one disease. Without depreciating the fact that there are also significant differences between upper and lower airway physiology and pathology, focusing on the common ground including patterns, triggers and interactions, is instrumental in achieving a 'holistic' management approach for our patients. Analysis can (and should) take over subsequently. Therefore, the term 'respiratory allergy' has been selected to include both the lower and upper airways and implies that allergy, in its broadest sense, is the major underlying

pathophysiology. To make certain the message may reach a wide audience, asthma and allergic rhinitis have been added in parentheses to the title.

In describing current and future research trends, one must first identify the major problems that require solutions. Many scientific and clinical questions exist and these will be described below. There are also conceptual issues which should not be neglected as they have the potential to drive research design, funding and interpretation. An example of this is the view of children as small adults resulting in less research being directed at this group. Another undesirable consequence is that children, and particularly infants, are the last group to benefit from scientific progress. For this reason, the European Parliament has encouraged pharmaceutical

companies to develop medicines specifically designed for children (1). An additional problem is the use of non-proven treatment strategies by extrapolating from adult studies. At least some of these approaches may have suboptimal results leading to skepticism and resistance in the pediatric community. The need for more child-focused research, as well as the inclusion of age and development as major milestones in defining phenotypes of asthma and allergic rhinitis, is emphasized by the international Pediatric Allergy and Asthma Consortium. In this article, present and near-future trends are merged into thematic paragraphs.

Definitions

Definitions are crucial in establishing a basis for further communication and progressing this area of clinical need. Several discrepancies with respect to epidemiology, natural history, mechanisms and treatment can be traced back to diverse or unclear definitions; this is true for both asthma and allergic rhinitis in childhood.

There is currently consensus that asthma is not a single disease but a syndrome encompassing several overlapping but distinct pathophysiologies that may vary in natural history and response to treatment (2). Reflecting the above, definitions are wide, including symptoms (e.g., wheeze), mechanisms (airway obstruction, inflammation), and/or triggers (3, 4). A major open question is whether 'all that wheezes' is asthma or not (5). Both Global Initiative for Asthma (GINA) and the more recent Practicing Allergology (PRACTALL) consensus, avoid taking strong positions, due to the paucity of data and considerable overlap (3, 4). In both cases, however, the importance of age is highlighted: infants, pre-school age children and older children (possibly adolescents as well) should be considered as separate groups. A feature of childhood asthma literature is that the term 'phenotype' has been used extensively in an epidemiological, rather than clinical sense, based upon findings from the Tucson study (6). This has helped to identify a subgroup of children who wheeze early in life due to reduced airway caliber (transient early wheezers) but has also generated some confusion related to cross-sectional evaluation of disease patterns. In contrast, adult studies are currently scrutinizing phenotypes at the pathological level (7). Recognition of phenotypes relevant to clinical practice may greatly facilitate the management of childhood asthma and may also stimulate research focused on particular clinical presenta-

tions. PRACTALL suggests the use of trigger-based clinical phenotypes (8).

Another important area is the definition of acute exacerbations of asthma. Exacerbations are relatively resistant to treatment and can be a result of mechanisms additional to the ones leading to chronic asthma. An American Thoracic Society/European Respiratory Society (ATS/ERS) taskforce, as well as a GA²LEN work package, are currently looking into optimal functional definitions (9).

In contrast to asthma, the definition of allergic rhinitis is much more narrow and, according to Allergic Rhinitis and its Impact on Asthma (ARIA), requires in addition to symptoms both a specific pathophysiological pathway (IgE) and specific class of triggers (allergens) (8). Therefore, the definition is more precise but it excludes numerous cases of 'non-allergic' rhinitis. This is a particular problem in infants and young children who suffer from repeated episodes of infectious rhinitis and have IgE sensitizations which in some cases do not seem to be clinically relevant. Although allergic rhinitis is the upper airway counterpart to asthma, chronic disease activity has not been separated from 'exacerbations' and there is currently no definition of a 'rhinitis exacerbation' (9). The extension of rhinitis definitions, as proposed by ARIA is required, in order to include non-allergic forms, as the relevant information is little and management not dissimilar.

Lastly, the definitions and distinctions between atopy, allergy and hypersensitivity and the contribution of each to specific clinical phenotypes are still poorly understood by clinicians despite the existence of consensus statements in this area (10).

Epidemiology

There is no doubt that childhood asthma and allergic rhinitis are highly prevalent diseases worldwide. The difficulties in definitions mentioned above may partly explain the wide variability in prevalence that has been consistently observed between and within studies. Extensive and reliable information comes from the International Study of Allergy and Asthma in Childhood (11). In the latest published results from this study, the global trend was toward an increase in allergic diseases (11). In some 'westernized' countries, with the highest historical prevalence, this trend seems to have now stabilized or reversed (11, 12). It is, however, unknown whether such a changing trend, if confirmed, reflect a plateau due to genetic resis-

tance in a proportion of the population, environmental changes or improved clinical management. The between and within country variability remains remarkable.

Attempts to explain some of this variability through presumed risk factors has been unsatisfactory. 'Western' lifestyle, a rather wide and imprecise term, has been very frequently quoted as a major risk factor. This cannot explain high prevalence in some South American countries (11). Similarly, higher socioeconomic status and urban vs. rural environments have frequently but not consistently been proposed as major risk factors. The exception is early exposure to farms which is negatively associated with allergy and asthma in several but not all studies (13). Associations have been seen with diet (14) but attempts for dietary intervention have had relatively poor or inconsistent results. Pollution seems to affect asthma activity but its effect on the development of asthma is not as clear. A consistent association is that of gender: asthma is more frequent in boys during early childhood while during adolescence the female proportion increases leading to higher proportion of women in adult life.

Tobacco smoke is another proven risk factor. A recent report from the U.S. Surgeon General clearly concludes that passive exposure to tobacco smoke in childhood, both during pregnancy and early in infancy, is causally related with cough, phlegm, wheeze and breathlessness, asthma and impaired lung function in childhood (15). Government programs aimed at reducing smoking in public paradoxically put children at greater risk of exposure to the long-term effects of tobacco because their parents may increase their consumption of cigarettes at home (16).

Atopy is very frequent among children with asthma and is always present (by definition) in allergic rhinitis. Exposure to allergens may increase, decrease or not affect the development of atopic sensitization and subsequent allergic disease, depending upon predisposition, timing and level of exposure.

In conclusion, asthma and allergic rhinitis are highly prevalent disease affecting at least one-third of the population (3, 4, 8). Risk factors have been identified but are probably subject to complex gene–environmental interactions. Improved methodologies for identification and quantization of such factors, as well as development of mathematical tools for the analysis of their interactions are needed. We propose the term 'environomics' to describe the integrated approach of assessing and evaluating the effects and interactions of multiple environmental fac-

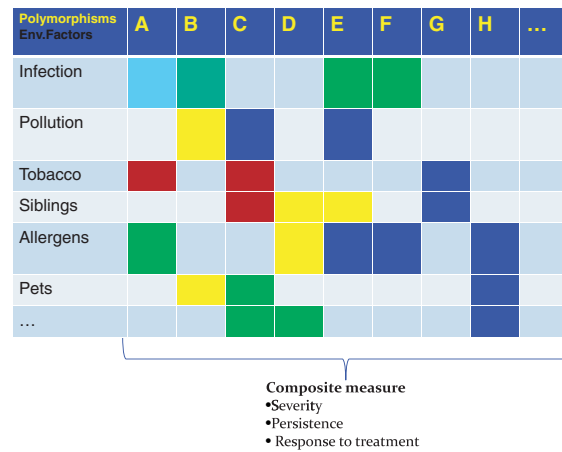


Fig. 1. An examination of the interaction of environmental factors and genetic predisposition may offer a new insight into the pathogenesis of atopic diseases. We have coined the term 'environomics' to describe this approach.

tors on physiological outcomes. In a subsequent step, combining genomics and environomics may give a picture representing gene–environmental interactions (Fig. 1).

Natural history

It is generally accepted that asthma starts early in life. Allergic rhinitis, partly due to its more strict definition, becomes clinically apparent somehow later on in life. Disease initiation is thought to be partly affected by genetic predisposition and partly by environmental exposures. The current model emphasizes the importance of phenotypic plasticity, i.e., the ability of a gene to give rise to contrasting phenotypes depending upon the environment (17). Such gene–environmental interactions are likely to be the next important step in asthma and rhinitis research. The importance of early life (or even pre-natal events) is increasingly stressed. Recent studies have shown that the major pathological characteristics of asthma, collectively referred to as remodeling, may be present in young children (but not infants), even before a doctor diagnosis of asthma and also in atopic children without any asthma symptoms (18). Other studies have consolidated our knowledge of major components of asthma inception: low lung function at birth increased the risk for asthma and airway hyperresponsiveness at the age of 10 yr in the Oslo cohort (19). Changes in lung function and airway responsiveness seem to occur in the first years of life; after school-age, lung function tracks until adolescence (6). In the Multicentre Allergy Study (MAS) study, lung function and airway hyperresponsiveness at the age of 13 yr were shown to be

affected by early allergic sensitization and exposure, for example, 90% of non-atopic wheezers lost their symptoms and retained normal lung function at school age (20). Furthermore, effects of early viral infections, that are associated with the persistence of asthma (21), seem to be more prominent in atopic individuals (22, 23).

Disappointing findings came from several independent studies showing that early therapy with inhaled corticosteroids is not able to alter the natural course of the wheezing illness (4, 24, 25). Nevertheless, it will always be the vision and task of pediatric research to look into prevention. Therefore, it is certain that other treatment strategies, either pharmacological or

environmental modification, will be pursued. Immunomodulation is also increasingly receiving attention.

The close association of asthma with allergic rhinitis has been demonstrated from various perspectives (8), however, such an association is not as clear in the case of pre-schoolers (1) suggesting the need for improved understanding and more precise definitions as stated above.

A considerable proportion of children with asthma will continue to wheeze in adulthood; risk factors include female sex, early onset, IgE sensitization and impaired lung function (26). More precise predictors are clearly needed (Table 1).

Table 1. Selected topics and questions of current research interest in respiratory allergy

Research topic	Open questions	How to address questions	Expected outcome
Identification of phenotypes of pediatric asthma	What are the types of asthma and rhinitis in children? What are the risk factors, pathogenesis and mechanisms of these phenotypes?	Improve the physiologic and clinical characterization of children with asthma Determine whether there are genetic and/or environmental factors that predispose to specific asthma phenotypes Develop biomarkers for specific asthma phenotypes	Better understanding of the phenotypes, evolution and prognosis Development of phenotype-specific treatment strategies
Prevention of remodeling	Can treatment change the natural course of the allergic respiratory disease? Can treatment prevent the deterioration of lung function?	Clinical trials using other asthma therapies (e.g., Leukotriene receptor antagonists, anti-IgE), specific Immunotherapy with different allergens and/or combined strategies	Reduce the incidence of severe asthma
Role of viral infections in the development of asthma	Can antiviral approaches (medications, vaccinations) reduce the risk of developing childhood asthma?	Identify at risk children in early life Develop efficacious and cost-effective antiviral approaches	Understand whether virus-induced wheezing in early life play a causal role in the development of asthma
Immune regulation of allergies and asthma	What is the normal pattern of immune development and what goes wrong during the inception of allergic diseases and asthma?	Conduct prospective studies of immune development and the onset of atopic disease Develop new techniques for measuring pediatric immune development, particularly in the airways	Understanding the patterns associated with health and disease should provide targets for future therapies and prevention
Gene–environment interactions	How do genetic polymorphisms interact with specific environmental exposures to modify the risk of chronic atopic disorders?	Conduct large observational studies employing a combination of genomics and ‘environomics’	Insight into asthma pathogenesis that should allow the development of new preventive strategies
Mechanisms by which exposure to specific allergens affects the etiopathogenesis of allergic respiratory disease	Is enzymatic activity is important in determining allergenicity? What properties of specific proteins promote allergenicity? Are there environmental factors acting as adjuvants for sensitization?	Conduct large observational studies focusing on how these factors impact on asthma expression Determine whether enzymatic activity is important in allergenicity Interactions of allergens–viruses–irritants (secondhand smoking, pollution, etc.)	Identification of the important factors will enable us to provide better information to our patients leading to better asthma control. Identify additional strategies for primary prevention of allergic diseases
Cost-effectiveness of treatments	How do we improve the identification of patients who will response best to different treatments or combinations of treatments?	Development of pharmacogenomics Multifactorial diagnostic tools (combining different clinical, functional, biological, Quality of Life, etc. outcomes, appropriately balanced)	By individualizing therapy, we should be able to improved children's asthma control while minimizing their exposure to therapies that are ineffective for their particular asthma. Target more expensive therapies to specific subgroups of children who are most likely to benefit

Mechanisms

Progress has been made in understanding mechanisms that underlie the initiation and disease activity of allergic rhinitis and asthma. Both diseases have hereditary and environmental components, as well as acute and chronic inflammation. Respiratory viral infections are closely linked to acute wheezing in asthma and may also contribute to the development of the disease. There is less information about how upper respiratory infections affect the onset and clinical course of allergic rhinitis. Genetic studies, which are more plentiful for asthma than rhinitis, have established a high rate of heritability within families (27). These studies confirm that asthma is influenced by polymorphisms in immunoregulatory genes that can regulate IgE or eosinophilic inflammation (17). In addition, positional cloning studies have identified candidate genes for asthma that suggest entirely new mechanisms related to signal transduction, mechanisms of tolerance and airway remodeling (1, 28, 29). Recently, both asthma and atopic dermatitis have been linked to polymorphisms in the FLG (filaggrin) gene, which contributes to epithelial integrity (30). This provides a genetic basis for the well-known clinical association between these two components of the 'allergic marathon'.

Epidemiologic studies indicate that the environment, particularly elements of a pastoral lifestyle and contact with animals, may help to direct immune development in such a way as to reduce the risk of atopic disorders such as rhinitis and asthma (13). These studies lend support to the hygiene hypothesis and have prompted research efforts involving animal models, *in vitro* studies and translational research to determine how stimulation of the innate immune system in early life might alter the risk of allergic sensitization vs. tolerance. Children are likely to be especially susceptible to environmental exposures, both favorable and noxious, due to the large changes in the immune system and airways during the first few years of life (21).

There are several examples of gene-environment interactions that affect the risk of asthma and allergic sensitization. For example, interactions with the CD14 gene have been studied extensively and the results suggest that specific haplotypes of this gene can be associated with either a low or high risk of asthma depending on the amount of endotoxin in the environment (31). Environmental factors that have been implicated in interactions with genes include innate immune stimuli, pollution, day care and viral infections (32).

As indicated above, investigation of inflammatory mechanisms originally focused on the mechanisms of skewing T cell responses toward a Th2-like bias. Several lines of investigation have shed new light on this process. For example, early life exposures influence the development of dendritic cells, which in turn provide cognate signals and cytokines that regulate antigen-driven T cell differentiation (22). The proinflammatory signals from dendritic cells and elements of the innate immune system are balanced by specific sets of T cells that express the transcription factor FOXP3, regulate inflammation and help to establish and maintain immunologic tolerance (33). Imbalances in the relationship between proinflammatory and tolerogenic immunoregulatory pathways are likely to contribute to chronic atopic diseases.

Asthma is often associated with an aberrant immune response to allergens and there is evidence that immune responses to respiratory viruses are also abnormal. Interestingly, low mononuclear cell interferon responses are a risk factor for both atopy and virus-induced wheezing in infancy (34, 35). Furthermore, interferon responses of lower airway epithelial cells may be impaired in asthma (36, 37). These findings could relate to the development of asthma in early life and also to the pathogenesis of asthma exacerbations. Recurrent respiratory infections, as a consequence of suboptimal antiviral defenses, could injure the airway at a critical stage in development and so increase the likelihood of permanent changes in airway structures that promote chronic lung diseases such as asthma.

Many allergens have enzymatic properties (38). The role of such allergens on the disruption of the respiratory mucosa and the increase of the permeability for other allergens, bacteria and viruses and other irritant substances deserves further and extensive investigation (39, 40).

A major proportion of asthma and rhinitis mechanistic research has not yet incorporated thoroughly the developmental aspects of the immune system. Immune responses change dramatically with age and many of the clinically observed differences in respiratory allergy expression in children may be affected by such changes.

Comorbidities

Asthma and allergic rhinitis are commonly associated with comorbid problems in contiguous structures, including allergic conjunctivitis, sinusitis and otitis media (41–43). The connection between allergic rhinitis and asthma is clear and

can be explained by mechanical (disturbance in the beneficial role of conditioning the air by the nose, post-nasal drip), neural (nasobronchial reflex) and immunological mechanisms. There is evidence that having concomitant allergic rhinitis may have a detrimental effect on asthma control resulting in the greater use of asthma related resources. There are also indications that treating allergic rhinitis may result in better asthma outcomes (43, 44). Additionally, children with asthma display symptoms in other organs (45, 46). Nevertheless, the epidemiology, mechanisms and organ-specific determinants are not as clear in the case of other respiratory entities. The conjunctiva is an important target organ in a proportion of patients with rhinitis and, when present, increases the specificity of the diagnosis. Otitis media with effusion has been shown to be independently affected by IgE sensitization, nasal symptoms and wheezing (47). Sinusitis is an important concern in adults, associated with severe asthma; the effects of sinus involvement in children require more attention.

Together these interrelationships support the concept of 'allergy as a systemic disease' and consequently the need for an integral diagnostic and therapeutic approach.

Diagnosis

Asthma has recently been defined as a complex dynamic model, beyond the classical diagnostic approach based on functional parameters, implying that the use of lung function alone may underestimate the complexity of the disease (48). Nevertheless, clinical history remains the cornerstone for diagnosis.

In the last few years, control and quality of life have become crucial parameters in diagnosis and monitoring of asthma and allergic rhinitis. The need to be sensitive to the perceptions of patients and parents seems crucial for the improvement of adherence to treatments and to improve patient satisfaction. Functional tests are more important in asthma; the considerable variability in functional tests for rhinitis limits their practical value. Very recently, an ATS/ERS statement addressing important issues in the evaluation of respiratory function in children, particularly small children, has been published (5). Measuring lung function in children is a major challenge, as they are frequently unable to voluntarily perform many of the physiological maneuvers required for the pulmonary function tests used in adults. Techniques such as forced oscillation, interrupter resistance, specific airway resistance and functional residual capacity using gas dilution tech-

niques are now feasible and may be very useful in asthmatic children. However, much work remains to be undertaken in standardizing the way in which these tests are performed and in understanding the most appropriate role for the various tests in the study of growth and development of the respiratory system and in the clinical management of children (5).

In addition, we are currently witnessing a growing interest in the study of the inflammatory substratum of allergic diseases. However, the need to use non-invasive methods limits their application in children. The analysis of exhaled nitric oxide (49, 50) may be quite useful (51) and is rapidly getting closer to bedside. Various inflammatory mediators in exhaled breath condensate are also promising, even though there are still many aspects that need to be elucidated (52).

The improvement in allergy diagnosis, including quality of extracts used for both *in vivo* and *in vitro* tests, the discovering of new allergens and the availability of wider allergen panels may permit an improved etiological diagnosis, which is critical for therapy. Allergy chips using wide panels of recombinant allergens may prove to be the diagnostic tool of the next generation. Nevertheless, interpretation of such tests remains complicated, physicians need to be trained in their use.

Finally, there is a need to develop and validate composite measures, including lung function, inflammation, symptoms and effects on quality of life, to enable us to take advantage of the increasing quantity of available information.

Treatment

A PRACTALL Consensus report on Diagnosis and Management of Childhood Asthma has been recently published (4). This document focuses on pediatric asthma and updates the new evidence on its management.

The classes of medications already in use seem to have stabilized. Although new, improved agents are appearing, it is difficult to predict when a next-generation therapy will be available in pediatric clinical practice. Pharmacogenomics are also on the horizon, not currently being specific enough for clinical use.

Inhaled corticosteroids remain the cornerstone of therapy. Leukotriene receptor antagonists have now proved beneficial for treating both allergic rhinitis and asthma concomitantly (53, 54) and have recently gained more attention in post-viral wheeze (55). A controversy exists on the effectiveness and safety of long-acting beta 2 agonists in children, although these agents have been shown to act synergistically with inhaled

corticosteroids in adult asthma. The paucity of studies in children, and the absence of those studies in pre-school children, together with some concerning safety data related with their use, clearly limiting their use in the pediatric population. This topic requires more studies focusing on individual and phenotype responsiveness and different outcome measures.

Virus-targeted therapies may prove important in the prevention or control of asthma exacerbations. Unfortunately, antivirals that are safe to use with asthma are currently, and for the foreseeable future, unavailable.

Macrolide antibiotics have long been known to have anti-inflammatory effects, in addition to their antibacterial properties. Although the evidence on their action in pediatric asthma is scarce (56), the recently shown effectiveness of the ketolide telithromycin on acute exacerbations of asthma may revive interest on these agents (57). Only a small number of biological therapies have managed to get into clinical practice, in part due to their high costs. An example is anti-IgE therapy which is able to control symptoms, improve quality of life and reduce asthma exacerbations in patients with concomitant asthma and allergic rhinitis and it is a plausible option for treating these patients, particularly those with the disease at the moderate to severe range of the spectrum (9). There is currently little published evidence about the efficacy of anti-IgE therapy in pediatric patients. Taking into account that this form of treatment is indicated in patients with severe forms of asthma, it is possible that its earlier use in children with less severe asthma might prevent the development of more severe chronic impairment. Consequently, studies addressing the characteristics of patients that would permit the selection of those in whom the use of this therapy would be cost-effective and efficacious in the long-term should be implemented.

Due to the reasons mentioned in the introduction, it is important to explore the possibilities for systemic treatments that will deal with respiratory allergy as a whole. There are studies showing benefits of intranasal corticosteroids on asthma symptoms and exercise-induced asthma (58). A recent study carried out in patients with concomitant asthma and allergic rhinitis older than 6 yr suggests that treatment with either nasal corticosteroids or second-generation antihistamines was associated with a significant reduction in the risk of hospitalization for asthma and asthma-related emergency room treatment (59).

Furthermore, although recent studies clearly state that therapy with inhaled corticosteroids is

not able to alter the natural course of wheezing illness (4, 24, 25), whether this can be achieved with alternative strategies requires further investigation.

There is also evidence showing that immunotherapy can benefit lower airway function in patients with allergic rhinitis and that the early use of immunotherapy in children with allergic rhinitis may prevent the development of asthma (60).

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