State-of-the-Art Complementary Therapeutics for Asthma

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Statistics indicate increasing prevalence of asthma in industrialized nations, particularly in the United States in the last 20 years. The Centers for Disease Control and Prevention has reported increasing asthma prevalence since 1980, including increased mortality and racial and regional disparities in asthma-related emergency department visits, hospitalizations, and deaths.[1]

According to the 1998 National Health Interview Survey, asthma is one of the most widespread chronic disease conditions in the United States, with 26.3 million Americans having been diagnosed with asthma by a physician within their lifetimes and with an increased mortality rate of 55.6 percent while all-cause mortality rates have decreased 18 percent. (See Table 1.)[2]

Various reasons for this increase in asthma cases have been identified, ranging from air pollution to faulty genetics. The mainstream focus on asthma has also changed in the last 20 years, with a shift in understanding—namely, that asthma is a chronic inflammatory condition. With this new understanding, treatment focus has changed from reactive to preventive, with chronic long-term use of inhaled corticosteroids as the mainstay of therapy. Despite this shift in treatment focus, increasingly negative statistics about asthma continue to be reported.

With the advent of complementary medicine, physicians are now more prepared than ever to treat asthma effectively. Asthma is a disease process with numerous associated genetic, allergic, environmental, and nutritional components, with varying symptomatologies among individuals affected with this condition.

There is a vital need for today's physician to develop an awareness of asthma's many precipitating factors and to learn about the numerous complementary therapies available for treatment because it is obvious that mainstream asthma treatment and prevention are not capable of reversing the increasing morbidity of this disease. Factors such as air quality may appear to be outside of the physician's realm of manageable patient comorbid components, while other precipitating determinants may be addressed via nutritional, botanical, and lifestyle supplementation allowing for greater efficacy of pharmaceutical medications, when needed.

Asthma Pathogenesis/Pathophysiology

Asthma is a chronic inflammatory disorder of the airways in which several cells and cellular elements play a role, particularly mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells. The recruitment and activation of these cells and cellular components leads to recurrent symptoms, such as wheezing, chest tightness, and coughing, more so at night and early morning. Such episodes are associated with diffuse airflow obstruction that is amenable to treatment-induced or spontaneous reversal. Predisposition to this condition causes an associated increase in the already established bronchial hyperreactivity to various stimuli.

Asthma symptoms that appear in childhood are often associated with atopy, a susceptibility in which immunoglobulin E (IgE) is produced in response to typically benign environmental antigens (dust mite feces, animal dander proteins, fungi spores). Synthesized IgE antibodies then bind to receptors on various lymphocytes. Once the offending antigen binds to the Fab fragment of the IgE antibody, proinflammatory cytokines are released. Mast cell–released histamine and leukotrienes stimulate bronchial smooth-muscle constriction, usually within 1 hour of antigen exposure.

Eosinophils, in particular, release destructive elements, such as major basic proteins that damage airway epithelial cells directly, increase bronchial responsiveness, and promote degranulation by mast cells and basophils. In addition, leukotrienes released from eosinophils cause additional airway smooth-muscle constriction, increased vascular permeability, and further recruitment of additional eosinophils.

The Th2:Th1 Ratio Theory

It is a well-established fact that airway inflammation is the mainstay of asthma pathophysiology. That being said, however, inflammation is a nebulous descriptor in terms of the multiple workings of the immune system in asthma. Newer theories of pathologic inflammatory processes portray abnormally regulated CD4+ T-cell responses to normally benign antigens as the instigators of asthma-related inflammatory processes.

More specifically, the Th2 subset cell grouping of CD4+ T cells is implicated, producing interleukins (ILs)-4, -5, -6, -9, -10, and -13. These cytokines establish the recruitment and differentiation of mast cells, basophils, eosinophils, and B cells, where they play a major role in humoral immunity and the generalized allergic response.

Opposed to these functions, the Th1 subset of CD4 lymphocytes produce interferon-γ and IL-2, both of which are used to create immunologic reactions that are specific to cellular defense, as in the case of parasitic and viral invasions. Ideally, the cytokines produced by Th2 and Th1 cells are mutually antagonistic, establishing a relative balance in functions.

Table 1. Asthma Facts

Prevalence

- Asthma has been increasing since the early 1980s across all age, gender, and racial groups; asthma rates are higher among children than adults and higher among blacks than whites.
- Approximately 17 million Americans have asthma; 5 million are under age 18. Asthma is the most common chronic childhood disease, affecting slightly more than 1 child in 20.

Deaths

- 14 Americans die each day from asthma.
- Between 1979 and 1992, asthma death rates increased 58 percent overall.
- Asthma death rates for children under 19 increased 78 percent between 1980 and 1993.
- More females die of asthma than males; more blacks die of asthma than whites.

Costs

- The total cost of treating asthma in 1998 was estimated to be $11.3 billion, of which direct costs amounted to 7.5 billion dollars, while indirect costs were 3.8 billion.
- Hospitalization accounted for the single largest portion of the cost.
- Among children ages 5–17, asthma is the leading cause of school absences due to a chronic illness; this adds up to an annual loss of more than 10 million school days per year and more hospitalizations than any other childhood disease.
- Children with asthma spend an estimated 7.3 million days per year restricted to bed.
- For adults, asthma is the fourth leading cause of work loss, resulting in nine million lost workdays each year.
- Asthma also accounts for about 1.8 million emergency room visits and nearly 10 million doctor office visits each year.
- Asthma results in about a half million hospitalizations each year; more women are hospitalized for asthma than men, and blacks are hospitalized from asthma three and one-half times more than whites.

Ethnic Differences

- Blacks are three times as likely as whites to be hospitalized from asthma and three times as likely to die from the disease.
- Racial differences in asthma prevalence, morbidity, and mortality are closely related to poverty, urban air quality, indoor allergens, and inadequate patient education and medical care.

Source: Adapted from the Asthma and Allergy Foundation of America (AAFA), 1233 20th Street, NW, Suite 402, Washington, D.C., 20036.

It is theorized that signature asthmatic inflammatory processes are expressed as a result of unbalanced Th1 and Th2 cytokine production, with a dominant polarization toward a Th2 phenotype, as asthma is a well-known Th2-mediated disease.[3]

It is highly plausible that asthmatic inflammation is a result of Th2-mediated mechanisms or an imbalance between Th1 and Th2 cells. It has been observed that children born with a predominance of Th2 cell subsets are predisposed to allergic disease and asthma.[4] In addition, it is thought that administering factors that enhance Th1-mediated responses may restore the Th1:Th2 balance in susceptible individuals.

One study investigated the relationship between Th subsets and their relationship to their relative cytokines, serum total IgE, eosinophil count, and ventilatory function in patients with asthma. The Th2:Th1 ratio in patients with acute or stable asthma was increased significantly compared to subjects in the control (nonasthma) group, with Th2 levels significantly and positively related to IL-4, total serum IgE, and total number of eosinophils. Forced expiratory volume 1 $(FEV)_1$ level in the study subjects had a significantly positive relation with Th1 levels and a negative relation with Th2 levels.[5]

The Hygiene Hypothesis

Recent analyses of risk-factor patterns for allergic disease in Europe has lead to a causal theory for the increasing asthma epidemic; this theory is known as the hygiene hypothesis. It stipulates that advances in hygiene have removed a protective influence against atopy and asthma that was once provided by infectious exposures in early childhood.

This hypothesis has been questioned in the United States, where the largest sector of increasing asthma incidence since the 1970s occurs in the inner cities among minorities who are living in poverty with suboptimal hygienic conditions. When viewed from a historical perspective, the recent increasing trend in respiratory allergies among the less-advantaged in the United States may be explained as the consequence of several epiphenomena linked to Westernization (including declining exposure to foodborne and orofecal infections) that has moved downward from the richest socioeconomic strata to the poorest in the last 150 years.[6]

In regard to this theory, it has been suggested that exposing infants to factors that increase Th1 cells (infected siblings, day care attendance during the first 6 months of life, and avoidance of frequent antibiotic administration) may restore the T-helper subset balance, resulting in fewer incidences later in life of asthma and allergy. It appears that these exposures must occur prior to the first year of life to make a difference.

Experimental use of mycobacterial strains has demonstrated a shift from Th2-immune responses to Th1-immune responses, thereby preventing the allergy development in mice, as well as ameliorating autoimmune diseases characterized by Th1 responses.[7] It is interesting to note that both autoimmune and allergic diseases share a parallel increasing prevalence. Rebalance of the Th1- and Th2-subset cell ratios is a highly speculative theory because it does not explain fully the complete immunologic etiology of asthma and allergies.

Gastroesophageal Reflux Disease

Various associations between asthma and gastroesophageal reflux disease (GERD) have been elucidated in recent clinical investigations: The prevalence of GERD in people with asthma is generally higher than in people without asthma. Patients who have asthma with GERD have a higher risk of hospitalization for asthma symptoms. Asthma medications such as albuterol decrease lower esophageal sphincter pressure and esophageal contraction amplitude, while oral prednisone results in increased esophageal acid contact times, and respiratory symptoms correlate with esophageal acid introduction events.[8] These findings suggest the possibility of asthma medications acting as promoting factors in the development of GERD in patients with asthma.

It is estimated that incidence of GERD in children with asthma reaches nearly 50–60 percent and is higher than in the general population.[9] This is not a newly discovered association; however many studies are underway to determine the relationships between asthma and GERD because it is not clearly known which is the cause and which is the result.

Several hypotheses surrounding the GERD–asthma connection focus on how GERD can lead to bronchial obstruction and how obstruction can exacerbate GERD. The esophagus and lungs interact by way of various mechanisms; esophageal acid-induced bronchospasm may be provoked by a vagally mediated reflex in which distal esophageal acid causes airway reactivity; by neural enhancement of bronchial reactivity, whereby esophageal acid augments airway hyperresponsiveness; and by microaspiration, in which miniscule amounts of esophageal acid are inhaled, leading to airway reactivity.[10] Possibilities that asthma may predispose patients to GERD include autonomic dysregulation, an increased pressure gradient between the thorax and abdomen, bronchodilator medications, hiatal hernia, and abnormalities in diaphragm function.

Clinical trials utilizing antireflux medical therapy (e.g. histamine-2 receptor antagonists) have been largely inconclusive, producing no benefit to only modest reduction of only nocturnal asthma symptoms.[11] Other studies that have investigated the use of proton-pump inhibitors and antireflux surgery are currently in progress. Despite the mixed results from these studies, the medical literature is flush with studies that demonstrate a definite link between GERD and asthma. Treating asthma with H-2 blockers and proton-pump inhibitor medications brings to light the possibility of leaving patients with inadequate amounts of digestive acid to properly break food proteins down, potentially leading to increased allergenicity of foods, including decreased nutrient absorption.[12]

Food Allergy

Asthma can be one of the major symptoms of chronic food allergy, contributing to the total overall antigenic load of a patient. Food-mediated allergic reactions may become clinically apparent immediately or even hours to days later in a patient with asthma, manifested by specific production by mast cells of IgE antibodies to food proteins.

From 20 to 60 percent of patients with bronchoconstrictive symptoms are reported to develop these symptoms as a result of food ingestion.[13] One study demonstrated that the elimination of previously determined food allergens early in life resulted in decreased asthma symptomatology as well as inhibiting the progression of allergic tendencies (represented by decreased production of total and specific IgE) compared to a control group that did not undergo such eliminations.[14] Increased gastrointestinal (GI) permeability and GI symptomatology has been found in a larger percentage of patients with asthma compared to controls without asthma symptoms; this may partially explain the origins of food-related allergy symptoms such as asthmatic wheezing.[15] Clinically, identification and removal of known and suspected food allergens does provide some amelioration of asthma symptoms in certain individuals.

Table 2. Doses of Supplements and Botanicals for Treating Asthma

Supplements/Botanicals	Doses
Pyridoxine (vitamin B_6)	25–50 mg, twice/day
Ascorbic acid (vitamin C)	2000–3000 mg/day, in divided doses
Magnesium	250–300 mg, thrice/day
Essential fatty acids (EPA + DHA)	2000–3000 mg, in divided doses per day
Tylophora (*Tylophora asthmatica*)	*Dried tylophora leaves:* 200 mg, twice/day *Or, alcoholic extract:* 40 mg, twice/day
Coleus (*Coleus forskohlii*)	*Standardized extract containing 18% forskolin:* 50 mg, thrice/day

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Vitamin and Mineral Therapy

Pyridoxine

The active form of pyridoxine (vitamin B_6) found in the human body, pyridoxal 5′-phosphate, has long been known to be depleted by theophylline, a now rarely used asthma medication. Regardless of current or past theophylline use, patients who have asthma tend to have lower circulating levels of this vitamin and, in one study, supplementation with 50 mg of pyridoxine twice per day for patients with asthma resulted in subjective reports of dramatic decreases in frequency and severity of asthma attacks while taking the supplement.[16]

The study did not, however, indicate reasons for the apparent beneficial effects of pyridoxine supplementation. Another study placed 76 children with asthma on 200 mg of pyridoxine per day for 5 months. These patients reported significant reduction of asthma symptoms and reduced usage of asthma medications.[17] However, in another study, 9 weeks of treatment with 300 mg of pyridoxine produced no difference in peak expiratory flow rate (PEFR), FEV_1, or asthma symptom scores compared to controls.[18] Examples of studies such as these demonstrate the need for increased research in the realm of vitamin B_6 supplementation for patients who have asthma.

Ascorbic Acid

Reactive oxygen species are implicated in the disease process of asthma, as it has been previously demonstrated that specific allergens were able to initiate a neutrophil-derived respiratory burst in some allergen-sensitized patients with asthma.[19] Excessive exposure to reactive oxygen and nitrogen species provides hallmark oxidative stress, propagating damage in proteins, lipids, and DNA structures. Oxidative stress in the lungs of patients with asthma is not only caused by intrinsic inflammatory pathways; environmental exposures, such as air pollution and cigarette smoke, also contribute. Interventions designed to augment endogenous antioxidant defenses are strongly indicated as adjuvant therapy for patients who are suffering from allergic respiratory disorders.[20]

Ascorbic acid (vitamin C) is one of the key antioxidant vitamins that are abundant in the extracellular fluid that lines the lungs, and low vitamin C intake has been associated with pulmonary dysfunction. One study reported that patients with asthma had significantly less ascorbic acid in both the cellular and fluid-phase fraction of induced sputum, suggesting that deficiency of ascorbic acid may be a result of airway inflammation or may be a contributing factor in the pathophysiology of asthma.[21]

Children with asthma who live in Mexico City were given a daily supplement combination of 50 international units of vitamin E and 250 mg of vitamin C for 19 months. Pulmonary function tests were performed twice per week, with significant differences in forced expiratory flow (25–75) and peak expiratory flow between the test and control groups. These results suggest that antioxidant supplementation, most notably vitamin C, can modulate the impact of air pollutants to reduce their effects on patients, including that of ozone on children with moderate-to-severe asthma.[22]

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Consumption of antioxidants in foods as an asthma symptom preventative method has also been studied. Intake of citrus and/or kiwi fruit was a highly significant protective measure for reducing wheezing among children who ate fruit 5–7 times per week compared to children who ate fruit less than once per week. This protective effect was even evident among the group whose fruit intake was only 1–2 times per week compared to those who consumed fruit less than 1 time per week, although no clear dose–response relationship was elucidated.[23] It appears that even relatively low dietary doses of vitamin C are protective against asthma symptomatology in children.

Prophylactic administration of ascorbic acid for prevention of exercise-induced asthma is widely described in the medical literature, with most studies revealing that taking vitamin C produces moderately beneficial effects to reducing asthma symptoms caused by exercise but results in little change in pulmonary function tests. The main conclusions drawn from these studies are that vitamin C demonstrates a slight-to-moderate protective effect on airway hyperreactivity in patients with exercise-induced asthma.[24]

A wide review of studies that have investigated the use of vitamin C for treating asthma and allergy found that, among the significantly positive effects of this therapy, positive effects on pulmonary function tests, metacholine, histamine, or allergen broncho-provocation challenges, lymphocyte function and motility, and decreased respiratory infection incidence were produced. No benefits were noted in these studies regarding testing of cutaneous reactivity or more specific immunologic parameter measurements. This main study also showed that the majority of vitamin C–asthma investigations were short-term and only addressed the immediate effects of vitamin C supplementation on asthma symptoms.[25]

Magnesium

Magnesium and calcium play various roles in pulmonary structure and function. A magnesium deficiency leads to an enhanced action of calcium being that excess magnesium acts as a calcium antagonist. This is notable in patients with asthma as a result of an intracellular influx of calcium causing bronchial smooth-muscle contraction.[26] Myogenically induced action potentials and autonomic neurotransmitters can alter cytosolic calcium concentration. Increased action potentials will lead to higher cytosolic calcium concentrations, causing greater cross-bridge activity. Likewise, intracellular magnesium can modulate smooth-muscle contractions and inhibit calcium uptake directly, allowing for smooth-muscle relaxation. Magnesium works as a smooth-muscle relaxant, of which the micromusculature surrounding the bronchioles is comprised.

Theoretically, inadequate magnesium levels may contribute to asthma exacerbations.[27] It is of interest to note that, while overall calcium intake in the United States has increased in the past 20 years, magnesium intake has remained unchanged, while the asthma epidemic continues to grow. Magnesium is an important contributor to prophylaxis of asthma symptoms and intravenous magnesium is an accepted form of emergency treatment for acute asthma attacks. Magnesium acts physiologically as a calcium antagonist, allowing muscle relaxation to occur.[28]

Patients with chronic asthma were shown to be hypomagnesemic, and this was associated with airway hyperreactivity, wheezing, and general impairment of lung function in one study. In addition, this investigation revealed that patients who have chronic asthma and have lower stores of magnesium are hospitalized more often than other patients with asthma who have normal levels of magnesium. Hypomagnesemia was also associated with more severe asthma symptoms.[29] Erythrocyte magnesium concentration shared a significant inverse relationship with inhaled metacholine challenge in relation to bronchial reactivity and hypomagnesemia was prevalent in 40 percent of the patients with asthma in this study compared to 11 percent of controls who did not have asthma.[30]

Based on this information, correction and stabilization of magnesium levels in patients with asthma seems indicated. As a medical therapy, magnesium has a good safety record. Because magnesium is almost exclusively excreted by the kidneys, overdose levels of magnesium can only be anticipated in patients with renal disease, intestinal hypomotility, and chronic constipation.

Omega-3 Fatty Acids

The end-product metabolism of arachidonic acid (AA), a component of cellular membranes, produces proinflammatory 2-series prostaglandins and 4-series leukotrienes, which are highly active mediators of inflammation. AA is derived from the phospholipid layer of immune-cell membranes via phospholipase A-2 in response to immunologic stimuli. The cysteinyl leukotrienes C4, D4, and E4 are important mediators in asthma and are modulators of cytokine function, and they have been implicated in the pathophysiology of asthma via multiple mechanisms, while leukotriene B4 promotes leukocyte chemotaxis and less-potent bronchoconstriction.[31]

Immune cells that drive the inflammatory process contain high proportions of the n-6 polyunsaturated fatty acid (PUFA) AA in relation to low amounts of n-3 PUFA; the two fatty acids are structurally and functionally distinct.

Coleus has been used traditionally on the Indian subcontinent for treating asthma.

The n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in high proportions in oily fish and fish oils, produce anti-inflammatory activity and are indicated for preventing asthma symptoms throughout the medical literature. Supplementation with fish oil results in partial replacement of AA in inflammatory-cell membranes with EPA, resulting in decreased production of AA-derived inflammatory mediators. However, this response alone is not totally indicative of the beneficial anti-inflammatory effects of n-3 PUFAs. Both animal and human studies have indicated that other anti-inflammatory effects of n-3 PUFAs may occur downstream from cell-membrane composition alteration, such as suppressed production of proinflammatory cytokines and inhibited adhesion molecule expression occurring at the level of altered gene expression.[32]

In one study, dietary supplementation with fish oil for 10 months in 29 children with bronchial asthma resulted in decreased asthma symptom scores and response to an acetylcholine challenge in the treatment group with no changes in the control group.[33] Subjects in the treatment group received fish-oil capsules that contained 84 mg of EPA and 36 mg of DHA. The daily dosages of EPA and DHA were, respectively, 17.0–26.8 and 7.3–11.5 mg per kg of body weight (–1), while control subjects received capsules containing 300 mg of olive oil. No side-effects were noted.

Studies on fish oil consumption have revealed decreased lymphocyte proliferation, T-cell mediated cytotoxicity, natural–killer-cell activity, macrophage-mediated cytotoxicity, monocyte and neutrophil chemotaxis, major histocompatibility (class II expression) and antigen presentation, production of proinflammatory cytokines (ILs -1 and -6, tumor necrosis factor), and adhesion molecule expression.[34]

The studies described above demonstrate the ability of fish oil supplementation to inhibit the inflammatory process of asthma. Based on these findings, one would expect to see decreased asthma symptomatology and improved lung function with addition of fish oils to the diet. The majority of studies do not indicate an optimal dose, however most doses of fish oils both EPA and DHA range from 500 mg to 3 g per day. For people who are allergic to fish or who have trouble digesting oils, capsules or flax (*Linum usitatissimum*) seed oil may be substituted.

Botanical Medicines

Coleus (*Coleus forskohlii*) is a member of the mint family that has been used traditionally on the Indian subcontinent for treating asthma. The active component of the plant, forskolin, has hypotensive and spasmolytic properties.[35] Forskolin's mechanism of action involves its ability to activate the enzyme adenylate cyclase. This action increases the amount of cyclic adenosine monophosphate (cAMP) in cells, which produces various physiologic and biochemical effects, including inhibition of mast-cell degranulation and histamine release as well as relaxing smooth muscle.[36]

Some pharmaceutical approaches to asthma are designed to increase cAMP levels by using an agent that binds to receptors that stimulate adenylate cyclase (corticosteroids) and inhibits the enzyme phosphodiesterase, which is responsible for the breakdown of cAMP. One example is the methylxanthine-derived drug, theophylline, which has fallen out of favor as an asthma therapy because of its narrow therapeutic window.

Forskolin's effects on cAMP result in bronchial dilatation and asthma symptom relief.[37] In addition, forskolin may be of benefit to patients with allergic asthma because this compound's antiallergy qualities also include histamine release inhibition.[38]

Tylophora (*Tylophora asthmatica*), another botanical medicine that is native to India, has been shown to have antiasthmatic, anti-inflammatory and antianaphylactic properties.[39] These effects have been attributed to the plant's alkaloid constituents, tylophorine and tylophorinine.[40] For one study, 110 patients with asthma were instructed to chew and swallow 1 tylophora leaf each day for 1 week. At the end of the week, 62 percent of the test subjects reported moderate-to-complete relief of symptomatology and experienced a continued reduction of symptoms for several weeks following the study.[41] Another study revealed improvements in lung function and decreased nocturnal symptoms in patients with asthma, an effect that, again, persisted past the 7-day trial duration.[42]

Conclusions

Asthma, like other chronic disease conditions, has increased in incidence over the last 20 years. Mainstream therapy includes the use of β-adrenergic agonists to maintain bronchial patency, while corticosteroids are used to prevent the now well-addressed inflammatory component of asthma. Relatively new outlooks on asthma pathogenesis, such as Th2:Th1 balance theory and the hygiene hypothesis, provide exciting new opportunities from which to base new approaches to asthma therapy. Table 2 summarizes some of these approaches.

Continued investigations of complementary therapies for asthma are well-recommended, because many therapies are offering promising outcomes, based on preliminary research. Addressing asthma in a preventative manner, using common supplemental interventions, such as ascorbic acid, magnesium, and fish oils, as well as botanical medicines, offers significant benefits for preventing bronchial hyperreactivity and inhibition of the damaging inflammatory response. □

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