The Allergic Response

The allergic response is best characterized as a specific inflammatory response of the immune system against environmental agents that contact the skin or mucosa. The primary immune cells involved in allergic responses are IgE-receptor positive mast cells (embedded within tissues) and basophils (circulating in the plasma). When an allergen cross-links two or more IgE antibodies connected to a mast cell, a cascade of signals triggers the mast cell to immediately respond with a variety of inflammatory processes. The first, and most notable, is the release of preformed substances from granules within the mast cell. This process, known as degranulation, releases substances such as histamine, heparin, tryptase and several inflammatory cytokines into the surrounding tissues. Likewise, mast cells also begin to synthesize other inflammatory mediators such as pro-inflammatory cytokines (IL-1, IL-6), TNF-α, as well as pro-inflammatory prostaglandins and leukotrienes. These substances lead to capillary permeability, edema, chemo-attraction of more immune cells, vasodilation, and pain. Prevention of this allergic reaction requires some understanding of the process that leads to mast cell destabilization and degranulation.

Figure 1: Airborne Seasonal Allergens

Some of the most common, recurrent ailments suffered by Americans are allergic reactions. The symptoms experienced by nearly 40 million Americans with allergic rhinitis (red, itchy eyes, runny nose, sneezing, sinus headache) can be either seasonal, in the case of “hay fever” or perennial. While rarely life-threatening, allergic rhinitis leads to periods of general misery, sleep loss, and lack of productivity in industry as well as education. This overview will look at some of the common causes of airborne induced nasal allergies, with a focus on the cells and processes involved in the allergic response. A focus on non-pharmacological agents that may help prevent or alleviate the symptoms associated with allergic rhinitis will follow.
of calcium from outside of the cell, which is vital to membrane destabilization and cell degranulation. This calcium-dependent process is mediated through calmodulin and the phosphatase calcineurin. Different cellular pathways are responsible for triggering the formation of arachidonic acid derivatives, the de novo synthesis of cytokines and the formation of the powerful transcription factor NF-κB. Each of these pathways are well-known targets of anti-inflammatory or anti-allergy drugs.

**Common Allergens**

Allergens can be any substance (usually a protein), that can elicit an IgE-mediated response. From a clinical stand-point, airborne allergens can be classified as perennial or seasonal. Perennial allergens would include things such as mold spores, dust and dust mites, animal dander (especially cats), and specific chemicals (cleaning agents and certain powders). Some of these allergenic compounds are small enough to penetrate into the bronchial tree when inhaled and often trigger asthmatic reactions. Patients having allergic rhinitis symptoms lasting more than 2 hours per day for more than 9 months would be deemed to have perennial allergic rhinitis. The allergen is most likely something in their home or workplace.

Seasonal allergies will typically follow a predictable pattern based on the growing season. Figure 1 shows the typical pattern of pollens associated with seasonal allergies in the Midwestern United States. Pollen from many trees, grasses and plants are particularly allergenic due to the ease of which they become airborne.

The first major allergen of the season begins when trees begin to release pollen. Trees with little or no visible flowers have a higher pollen count since they rely on the wind rather than insects for pollination. The summer months are typically the time for grass pollen allergies. These can come from commercial crops such as corn, and are less of a problem in urban areas where grass pollinates less frequently due to frequent mowing. The fall is the most intense allergy season in the central U.S. due to the large amount of weed pollen that becomes airborne. Ragweed pollen, one of the most common allergens, has been recovered in the air above oceans, 400 miles off the coast. Other common weed allergens are the pollen of pigweed, sage brush, lamb’s quarter and certain thistles. Interestingly, the common term “hay-fever” is actually a misnomer since neither hay (alfalfa) nor fevers are typically associated with allergies.

Finally, there is the issue of fungal spores. As one can notice from figure 1, fungal spores are high at all times except during times of snow cover (typically late November through February). Fungal spores can be kicked up any time a person is walking through grass or leaves, cutting or stacking wood, or just being in a damp outside location. Fungal spores are so ubiquitous and long lasting it may be difficult to determine where the source of spores may be coming. In these cases, skin testing would be warranted to determine that indeed the patient is suffering from an allergen and is not experiencing infectious sinusitis.

**Allergic Susceptibility**

While reactions to airborne allergens are very wide-spread, certain individuals are much more susceptible than others. This is because a true allergic reaction requires that the individual have B-cells that produce IgE antibodies that bind to the allergens to which they are exposed. If the IgE antibodies cannot bind the allergen, or the allergen preferentially binds to other antibodies such as...
IgG (see immunotherapy section below), then the allergen is incapable of stimulating the mast cell pathways that trigger the allergic response. Since antibody shape is partially dependent on specific immunoglobulin genes, an individual’s genetics play some role in their susceptibility to allergic conditions. The dramatic increase in allergic disorders over the past 100 years cannot be explained by genetics alone, and is influenced dramatically by the “priming” of the immune system in early life.

B-lymphocytes are responsible for producing antibodies (immunoglobulins) and are influenced by a subset of T-lymphocytes called T-helper (Th) cells. B-cells that are stimulated by the Th2 subset of T-helper cells are more likely to produce IgE antibodies than B-cells stimulated by Th1 cells. Many factors can influence a shift in immune system Th2/Th1 ratio, including maternal diet and immune challenges during fetal development, early childhood exposure to antigens and allergens, diet, gut microflora and immunizations. The so-called “hygiene hypothesis” suggests that children with more exposure to pathogens earlier in life will preferentially develop a Th1 profile which results in less allergic susceptibility. The inverse relationship between atopic diseases and exposure to childhood pathogens seems to confirm the hygiene hypothesis, although the relationship is far from scientific agreement. Other factors that have been shown to be associated with increasing allergic potential are urban living, exposure to diesel exhaust, use of antibiotics, fewer siblings, and vaccination programs. Agents that shift the immune system away from Th2 responses will likely prove to lower the allergenic burden in most individuals.

**Prevention and Treatment**

Seasonal allergies are often predictable in many individuals and are frequently self-diagnosed and self-treated conditions. Over the counter antihistamines and decongestants are advertised and purchased widely during the common allergy seasons. Below we will outline the best ways to prevent and treat allergic rhinitis using natural ingredients which often have secondary benefits as anti-inflammatory agents, broncho-regulatory agents or immuno-regulatory agents.

**Avoidance**

Assuming one knows exactly what the offending allergens are, the most obvious and beneficial thing that a person can do is avoidance. Spending time in air-conditioned areas, including cars, will filter out many of the offending allergens. Additionally, some relatively cheap air filter/purifiers are able to remove many potential allergens. Using dehumidifiers to reduce humidity levels is another way patients can reduce moisture-related increases in indoor allergens such as dust mites and mold spores. For patients with dust mite allergies, reducing the number of dust collecting items in their homes (carpets, curtains, stuffed animals, cloth furniture) and the use of vacuum cleaners with HEPA filters will be advantageous.

Sometimes, however, a patient may not know what allergens are affecting them, or have not properly diagnosed their symptoms as allergy related; perhaps considering them to be associated with a cold or intermittent sinusitis. In such cases, identifying the offending allergen(s) is an important first step in avoidance prevention. Skin tests are often the simplest means by which to test cross-reactivity of common allergens. Since there are numerous mast cells within the layers of the skin, a dilute solution of a common allergen will produce a classic wheal and flare reaction when applied to a scratch on the skin of a sensitive person. A blood test called a radioallergosorbent test (RAST) can also be done which will detect the presence of IgE that cross-reacts with different antigens. Some labs offer different panels, many of which include common food allergens as well as airborne and contact allergens.

**Drug Therapies**

Antihistamines are often the first therapy used by allergy sufferers, as they are widely available as both OTC and prescription drugs. As the name of this class of drugs implies, antihistamines block the ability of histamine (one of the key preformed mediators within mast cell granules), to bind histamine receptors, relieving many of the histamine-related effects. By blocking the histamine receptors, antihistamines are used for reducing sneezing, itchy eyes and nose, and slowing the pace of a runny nose. One of the most popular (and typical) of the first generation of antihistamines is diphenhydramine (Benadryl®), which works by blocking histamine H₁ receptors. These older forms of antihistamines are lipophilic, allowing them to cross the blood-brain barrier and leading them to cause sedation, drowsiness and other related CNS side-effects. In fact, it is because of this side effect that many of the antihistamines are used as sedatives and hypnotics. Newer antihistamines, such as loratadine, cetirizine and fexofenadine, do not cross the blood-brain barrier, dramatically reducing potential sedating side-effects.
effects when taken at the appropriate dose, although they come with a much higher cost. These newer drugs are contraindicated in patients with impaired liver or kidney function and with the concomitant use of erythromycin (a common antibiotic) and ketoconazole (a common antifungal).

While antihistamines block many of the effects of histamine, they are unable to stop the mast cell from releasing histamine or any of the other preformed or lipid-derived mediators. This means that some of the secondary problems associated with allergies are unaffected or masked by antihistamines. Such problems as nasal congestion and asthma must be addressed by other means.

Another pharmaceutical option is topical steroid preparations. These glucocorticosteroids, supplied through nasal sprays, function much the same way corticosteroids alter inflammatory pathways. They are mainly indicated in long-term allergic conditions that are not responding to antihistamines, although they are sometimes combined with antihistamine therapy. Additionally, the asthma drug montelukast, which functions by blocking leukotriene receptors, has also been used as a monotherapy or in combined therapy with either antihistamines or topical steroids for allergic rhinitis and asthma.

Bronchodilators and decongestants are also available by prescription or as over-the-counter medications. The most common would be ephedrine or pseudoephedrine (Sudafed®) containing products. They work primarily as α-adrenergic agonists. They reverse congestion by vasoconstricting the blood vessels within the nasal mucosa, reducing swollen membranes allowing sinus drainage and improved air conduction. Since both ephedrine and pseudoephedrine also affect the β-adrenergic receptor, they are capable of acting as bronchodilators. Care should be taken when patients with heart conditions, high blood pressure, or on MAO-inhibitors take these drugs; and they should be limited to no more than a few weeks.

**Immunotherapy**

Allergen immunotherapy involves the subcutaneous injection of a dilute solution of the offending allergen in increasing doses over several months. Essentially, immunotherapy attempts to stimulate production of other types of antibodies (IgG especially) which will then proliferate and bind to the allergen in the place of IgE. Since IgG antibodies do not have receptors on mast cells, they will not stimulate an allergic response. It is not uncommon for many people to take “allergy shots” at regular intervals throughout the year and may require years of therapy for long-term benefit. Sublingual immunotherapy treatments are also available and may prove to be similarly beneficial when compared with the more long-standing subcutaneous injections.

**Diet and Allergy Risk**

Foods have a profound effect on the immune system and can influence the relative risk of allergic rhinitis (as well as food allergies themselves, which is beyond the scope of this article). Eating foods rich in anti-inflammatory compounds normally reduces the inflammatory and allergenic profile of an individual. For instance, diets high in omega-3 (n-3) fatty acids (EPA, DHA, ALA), reduce the risk of allergenic sensitization and symptoms associated with allergic rhinitis. This is true in both adults and children, and includes fish and fish oil consumption during gestation and breast-feeding.

Maternal fish oil supplementation (3.7 g/day n-3, 56% DHA) in atopic women (offspring considered at high risk for allergic diseases) significantly increased breast milk levels of the protective immunoglobulin A (IgA) and CD14. Children born from these mothers have reduced levels of allergic related cytokines and allergen-specific immune responses. Children at high risk for atopic diseases had reduced allergy-related cough at age 3 if they were supplemented with fish oil (500 mg of tuna oil/d- 185 mg n-3) from 6 months to 3 years. Eating high levels of n-3 fatty acids directly from fish is contraindicated in young children and pregnant women due to the potential for ingesting mercury and other toxins. Fish oil supplements, virtually free of these toxins, are safer and allow for specific dosing regimens. Many liquid as well as capsule preparations can be used which provide varying levels of DHA, some of which are specially prepared and flavored for children.

It is clear from numerous studies that children and adults who consume a variety of fruits and vegetables have a lower risk of allergic rhinitis and associated asthma. Carotenoids and flavonoids from fruits and vegetables are known to reduce the risk of allergy symptoms and likely account for much of the effect. The additional oxidatative burden during allergic reactions is also mitigated by providing antioxidants in the form of foods or supplements. In addition, maternal consumption of certain antioxidants, particularly vitamin E and zinc, reduce the risk of wheezing and eczema (atopic-related) in children at age 2.
Probiotics

It is well established that gut microflora has a profound influence on overall human health; and the use of health-promoting bacteria, known as probiotics, in fermented foods and dietary supplements is wide-spread and growing. While maternal and infant use of certain strains of probiotic organisms have shown a reduction in certain atopic conditions such as eczema, as well as a reduced IgE burden; the use of probiotics in the treatment of allergic rhinitis is relatively new. Several strains of probiotics have been shown to limit some allergic rhinitis symptoms, reduce allergen specific IgE and increase the ratio of Th1/Th2 cells. Interestingly, one study comparing live cells versus heat-killed cells (Lactobacillus paracasei - 5 billion CFU/capsule) showed that the improvements were not dependent on living organisms. These findings are not surprising, since other studies have shown the ability of heat-killed organisms to stimulate Th1-related cytokine production and reduce IgE production. More studies are being conducted to determine which strains of probiotic organisms preferentially promote the Th1 pathways while down-regulating the Th2 pathways. The overall benefits of consuming probiotics through dietary supplements or fermented foods should lead most physicians to recommend them to patients suffering from allergic rhinitis.

Quercetin and Related Flavonoids

Flavonoids are the general term used to describe over 4000 different compounds in plants containing the flavone ring. These compounds are very diverse and include the flavones, isoflavones, flavanols, catechins, anthocyanidins and chalcones among others. They are among the most studied plant compounds and have been shown to have numerous clinically relevant biological activities. Among the flavonoids, quercetin and its closely related compounds have been widely studied for their mast cell modifying activities and related anti-inflammatory potential. Quercetin is the aglycone (non-carbohydrate portion) of rutin, quercetrin and other glycoside flavonoids and is widely distributed in the plant kingdom in plants such as oak trees (Quercus spp.), onions, and others.

Figure 3 shows the step by step process which triggers the allergic response and the resulting inflammatory mediators and pathways. Shown in blue are agents that are known to inhibit the allergic response at various stages of the process.
Quercetin's potential effects on allergy-related pathways is unmatched by other natural substances. Quercetin inhibits phospholipase A (responsible for liberating arachidonic acid from membrane phospholipids), lipoxygenase (responsible for converting arachidonic acid into leukotrienes), platelet aggregation, and mast cell and basophil degranulation. Quercetin has been shown to bind to calcium/calmodulin complexes, preventing the influx of calcium into mast cells and basophils. This inhibition prevents the mast cells from destabilizing and degranulating, keeping histamine and other preformed mediators from being released. In fact, quercetin so consistently blocks calcium induced mast cell destabilization that researchers often use it in experiments as a control substance for such activity.

In a recent study using cultured human mast cells, quercetin was capable of preventing the release of tryptase and histamine from stimulated mast cells, but in addition, inhibited the release of the pro-inflammatory cytokines IL-6, IL-8 and TNF-α. These authors showed that quercetin was capable of preventing calcium influx, a necessary precursor to degranulation, as well as preventing the phosphorylation of protein kinase C theta, the activity of which is not regulated via calcium but involved in mast cell allergic activation. Quercetin and related flavonoids have been shown to have numerous other activities related to mast cells and basophils, including the inhibition of Th2 cytokines, inhibition of the pro-inflammatory mediator monocyte chemoattractant protein-1 (MCP-1), and reduced levels of the mast cell enzyme responsible for histamine production, histidine decarboxylase.

The activity of quercetin and other flavonoids have been well known for years, leading to the synthesis of similar compounds by pharmaceutical companies. One such compound, cromolyn sodium, has been used as a mast cell stabilizer for years. Since cromolyn cannot be absorbed orally it must be delivered as a powder through spinhalers or aerosol inhalers. Even then, only 8% is absorbed in the respiratory tract often leading to the need for 2 metered dosages four times per day.

Like most biologically active flavonoids, quercetin's pharmacology is quite interesting. The absorption of quercetin is about 20-52% depending on the form. Quercetin absorption is very predictable when consumed as an aglycone, but may vary by individual and gender if taken as a glycoside, such as rutin. The elimination of quercetin and its derivatives is slow, and high plasma levels are easily maintained with a regular supply of quercetin in the diet.

that more than 25% of the absorbed quercetin was localized in the lung tissue, an added benefit to combat allergy and associated asthma. While these radioactive studies have not been repeated in man, it is likely that similar results would be found. It has been known for some time that the concomitant administration of bromelain, an enzyme derived from the stem of the pineapple plant, can enhance the absorption of quercetin as well as other flavonoids such as rutin. An added benefit included with bromelain is its ability to block inflammatory pathways (fibrin and kinin) and decrease the viscosity of mucus in the lungs.

Patients should begin to take quercetin (available in capsules or tablets) upon the first signs of allergen exposure. Since quercetin acts prophylactically (stabilizing mast cells rather than blocking histamine receptors) and will stay in the blood stream, initial doses should be 400-600 mg, three times per day, for the first 5-7 days. Symptom relief may begin in the first several hours. Once plasma levels increase, 200-400 mg per day may be sufficient through the rest of the allergy season, depending on exposure. Quercetin is extremely safe, and includes many other documented benefits (antioxidant, anti-inflammatory, capillary stability etc.) and should be considered part of the foundation of any natural approach to allergic rhinitis therapy.

**PETASITES**

Petasites (Butterbur, Petasites hybridus), is a perennial shrub in the Asteraceae family; native to Europe, Northern Africa and parts of Asia. Extracts of both the leaf and the root are commercially available and have become popular for their use in alleviation of pain, especially related to migraine headaches. Compounds found in the active fractions of petasites, called petasines, are known to inhibit leukotriene formation and have also been shown to alleviate bronchial asthma and allergies.

A leaf extract (CO2) of butterbur called Ze339, delivered in tablets, has been shown to improve allergic rhinitis symptoms in a dose-dependent manner when compared with placebo. Previously, this same extract (4 tablets per day delivering 32 mg of petasine) was shown to be comparable to 10 mg cetirizine in patients with allergic rhinitis. Two different extracts were comparable to fexofenadine (180 mg/day) in subjects with perennial allergic rhinitis. In a skin test; however, it was shown that butterbur extracts do not inhibit the mast cell degranulation process or histamine release from mast cells. This data suggests that butterbur acts on pathways similar to the anti-leukotriene drug montelukast, and is not functionally comparable to antihistamines or mast-cell stabilizers.
**Nettles**

Among the many plants one would propose to be helpful in the treatment of allergic rhinitis, the stinging nettle (*Urtica dioica* L.) would probably not be among them. This common plant, often called “itch weed”, is known to cause hives or urticaria (hence the Latin name) due to the histamine located in needles under each leaf. However, for years the dried leaves of stinging nettles were used for the symptoms associated with allergic rhinitis. Finally in 1990 a double-blind, placebo-controlled study was done to assess the use of stinging nettle leaf for allergic rhinitis.68 After one week, stinging nettle was rated higher than placebo. Unfortunately this study was based on diary entries of symptoms and overall patient ratings. These studies should be expanded to include more patients, longer intervals, and more objective measurements.

For many years the mechanism for nettles’ anti-allergy and anti-inflammatory activities were unknown, although some speculated a homoeopathic-type affect due to latent histamine in the dried plant material. A recent article studying the use of stinging nettle leaf extracts in the treatment of rheumatoid arthritis may help explain the mechanism. An extract of stinging nettle leaves was shown to inhibit both lipooxygenase and cycloooxygenase activity.69 These two enzymes are responsible for converting arachidonic acid into pro-inflammatory prostaglandins and leukotrienes. Additional studies on the role of nettles leaf extract and its constituents have been conducted, although follow-up studies on the direct role in allergic rhinitis need to be confirmed.70,71 Nettles leaf should not be confused with nettles root extract, which is used primarily for its affects on prostate hyperplasia.

**Other agents**

Many other complementary and alternative medical approaches have been used with varying success. These include numerous single herb or herb combinations from various botanical and homeopathic drug traditions. Passalacqua et al. have recently reviewed these clinical approaches, along with research into other modalities such as acupuncture, chiropractic and other physical techniques. Some of the agents with limited positive clinical data include MSM (2600 mg/day),72 apple polyphenols (220 mg/day),74 extract of *Tinospora cordifolia* (900 mg of standardized extract per day),75 and Aller7 (a multi-herb formula).76

**Natural Bronchodilators and Mucolytics**

Asthma is one of the most common allergy-associated consequences. It can be triggered by the same events as allergies (IgE-allergen interaction) and results in the constriction of the bronchioles and increased production of bronchial mucus. While several of the mast cell preformed mediators play significant roles in asthma, increasing research has been targeting leukotriene and platelet activation induction with asthma risk.77-79 These lipid-derived mediators are responsible for drawing eosinophils (by chemotaxis) to the lungs, which perpetuates the response by releasing more platelet activating factor (PAF). Several botanical constituents, including quercetin80 and bilobide B from *Ginkgo biloba*,81 have been shown to inhibit the synthesis or effect of PAF.

*Ephedra (Ephedra sinica Stapt.) or Ma Huang has been used in Chinese medicine for thousands of years.*82 The ephedra plant contains 2-3% alkaloids, mostly ephedrine and pseudoephedrine. These alkaloids were discovered and synthetically produced in the late 1920’s and their use has been wide in over-the-counter and prescription medications for asthma, hay fever and related conditions. These compounds are very effective bronchodilators.

Ephedra has come under scrutiny by the FDA, primarily due to its formulation with caffeine-containing products and its promotion as a stimulant weight-loss product, and currently is unavailable as a dietary supplement in the United States. Extracts of ephedra (Ma Huang) can be safely used for short-term use (1-2 weeks), and may be available by practitioners of traditional Chinese medicine. Longer use of ephedra should be monitored closely and should be accompanied by adrenal stimulating herbs like licorice (*Glycyrriza glabra* L.), Siberian Ginseng (*Eleutherococcus senticosus* Maxim.), and Dandelion Root (*Taraxacum officinale* Wiggers). Ephedra extracts contain 6-8% ephedrine and should be dosed at 200-400 mg 2 or 3 times daily. Each individual reacts differently to ephedra and smaller and less frequent doses should be attempted prior to increasing dosing. Unfortunately, few other botanicals have shown consistent positive clinical use as a bronchodilator and not been able to replace the role of ephedra extracts.

N-acetyl cysteine, or NAC, is a potent natural expectorant/mucolytic agent, although its use has declined in recent decades. NAC has been gaining interest as an antioxidant that acts directly or as a “recharger” of the body's own glutathione.83 As disulfide reducing agents, both NAC and glutathione can decrease the viscosity of mucus, which
is increased by disulfide bridging of sulfur proteins in mucus during asthmatic reactions. Recently, the mucolytic mechanism is being reassessed by research suggesting a “mucoregulating” action for NAC.54,83 NAC has been used quite frequently in an assortment of lung conditions including COPD, bronchitis, and asthma.86 Recent data also suggest NAC inhibits the function of eosinophils, immune cells known to be active in allergy-induced asthma, as well as the immune recruiting chemokines expressed by smooth muscle cells of the human airway.87 Clinical doses range from 600-3000 mg per day in divided doses.89,90

**References:**


**Conclusion**

According to a report published by the American College of Allergy, Asthma and Immunology (ACAAI), a shortage of physicians specializing in allergies will prevalent over the next dozen years.92 This will increase the need for general practitioners and physicians trained in alternative medicine to deal directly with patients needing symptom relief for perennial and seasonal allergic rhinitis. As we have shown in this review, a number of lifestyle, diet and non-pharmacological approaches may provide superior symptom relief, compared to the available pharmaceuticals, with fewer side-effects. These approaches will also improve other health outcomes, as these agents have wider benefits as probiotics, antioxidants (flavonoids, NAC), immunomodulators and anti-inflammatory agents. The benefits of foods and dietary supplements, especially as combinations of many of the agents mentioned in this review, give the physician and patient many different options to find a regimen that will suit their particular health needs beyond their ability to eliminate the symptoms related to allergic rhinitis.

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