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Allergic respiratory disease is very common. The annual prevalence of seasonal allergic rhinitis varies from 5-22%. It has been estimated that 9% of all visits to physicians' offices are for one of the common allergic diseases. Seasonal catarrh, or hay fever, was first described by John Bostock as early as 1819. Treatment of inhalant allergens began around 1911, when Leonard Noon began treating his patients with injections of pollen extract on the assumption that "antitoxins" would be formed to neutralize supposed "toxins" released by the pollens. By 1940, serial dilutions for skin testing were begun.

Inhalant allergens remain the most familiar offenders for the allergy sufferer. These allergens are identified by their portal of entry rather than biological makeup. They enter via the respiratory tree, making their initial contact with the mucosal lining of the nose, mouth, and throat. Since the entire lining of this part of the body is richly supplied with IgE, it is not surprising that essentially all inhalant allergy is IgE mediated, producing an immediate Type I Gell and Coombs reaction.

Anatomy

Understanding the anatomy assists in the differential diagnosis and understanding the potential complications of the disease. The nasal septum divides the nasal cavity in half. The nasal vestibule funnels air towards the nasal valve, which is formed by the upper lateral cartilages, the nasal septum and the inferior turbinate. The nasal valve accounts for approximately 50% of the total resistance to airflow from the nose to the lung. The lateral nasal wall has 3 turbinates that increase mucosal surface of the nasal cavity to about 100-200cm². A thin, moderately keratinized, stratified squamous epithelium lines the nasal vestibule, changing to pseudostratified columnar, ciliated epithelium in the remainder of the nasal cavity. The neural supply is predominately sensory and autonomic.

Immunology

The immune system consists of lymphocytes, phagocytes, complement, and mediator cells and their products. It functions to distinguish between self and nonself and to eliminate that which is foreign to itself. The subsequent immune response can be beneficial or harmful.

Immunologic mechanisms of hypersensitivity are classified by Gell and Coombs into four types:

Type I- Immediate Hypersensitivity. The allergic reaction occurs within minutes of allergen exposure in a sensitized person. An allergen binds two molecules of IgE attached to the receptor site on the surface of a basophile or mast cell. This causes a release of chemical mediators from these cells. Examples include allergic rhinitis, anaphylactic shock, and asthma.

Type II- Cytotoxic reaction. Is also immediate and requires the binding of either IgG or IgM to the surface of the cell-bound antigen. This activates the complement cascade and results in lysis or agglutination of the target cell. Hemolytic anemia is an example.

Type III- Immune complex reaction. Antigen-antibody complexes combine with complement to form immune complexes that are deposited on tissue. Reactions occur several hours to days after exposure to antigen. Examples include autoimmune diseases, and serum sickness.

Type IV- Delayed Hypersensitivity. This type results in tissue injury involving presensitized T-lymphocytes. It is the basis for PPD testing.

On inhalation, pollens deposit on the nasal membranes where allergen elution and diffusion occur. Allergens are processed by antigen presenting cells and presented to T-helper cells and in turn to B cells. Interleukins, especially IL 4 and IL13 favor IgE synthesis by B cells. Allergen specific IgE then attaches to receptors on mast cells and basophils. The acute inflammatory process begins in sensitized individuals when an allergen binds to these specific IgE antibodies. This provokes cellular degranulation and release of preformed and newly synthesized mediators and cytokines. These mediators have immediate and direct effects on vascular endothelial cells, smooth muscle, nociceptive neurons, glandular cells and other inflammatory cells. Within minutes, these actions cause the characteristic symptoms of allergic rhinitis, including sneezing, watery nasal discharge, and itchy eyes, nose, and throat. The preformed mediator that is most active during this phase is histamine. It increases vascular permeability and glandular secretion and induces nervous reflexes, such as sneezing and nasal itching. Other mast cell mediators involved in this stage include prostaglandin D₂, bradykinin, leukotrienes, and platelet-activating factor.

Between the immediate and late phases, there is an asymptomatic transition stage that involves activation of endothelial cells and the recruitment of leukocytes into the nasal tissue from blood vessels. Cytokines play a key role in recruiting circulating leukocytes through their activation of the expression of adhesion molecules by endothelial cells. These molecules, such as vascular cell adhesion molecule, enable leukocytes to adhere to the endothelial surface. Cell-

specific cytokines are then responsible for the migration of these eosinophils, basophils, monocytes, and T-lymphocytes from blood vessels into mucosal tissue.

Local leukocyte infiltration is the hallmark of the late phase, which usually occurs within 4-6 hours after allergen exposure. The most dramatic changes in the nasal mucosa are caused by the cytokine-mediated influx and activation of eosinophils, basophiles, and T-lymphocytes. Cytokines such as cysteinyl leukotrienes and IL-4, IL-5, and IL-13 released from white blood cells may be among the most significant pro-inflammatory mediators to perpetuate the inflammation and nasal symptoms. Clinically, it is characterized by an increase in mucosal thickness and congestion, as well as rhinorrhea and sneezing that persist from early phase response.

Symptoms & Diagnosis

The history is the most important method of establishing the diagnosis of inhalant allergy. The symptoms in general are immediate in onset and clear quite rapidly with removal of the offending allergen. Details as to what symptoms occur, what allergen exposures the patient has, and what things appear to be causing symptoms provide the basis for allergy testing and environmental control measures. The symptoms are largely confined to the respiratory system and mucous membranes. Symptoms of allergic rhinitis may include congestion, rhinorrhea, postnasal drip, sneezing, itchy nose, watery eyes, headache, and loss of smell or taste. Itching of mucous membranes and repeated sneezing are the most distinctive complaints. Allergic conjunctivitis is manifested by lacrimation.

Physical exam findings may support the diagnosis of allergic rhinitis as well as rule out anatomic factors aggravating the allergic condition. The nasal mucosa tends to be pale, bluish, congested and covered by copious watery mucosa. Infraorbital edema and discoloration caused by venous stasis characterizes an "allergic shiner." Lymphoid hyperplasia is common, manifested by enlarged tonsils and adenoids and cobblestoning of the pharynx.

Analysis of the nasal secretions can be of significant diagnostic value in evaluating suspected inhalant allergy. The relative numbers and types of cells in the secretions are noted. Many areas of the nose have been sampled and surveyed. The inferior turbinate is the most representative. The material is then immediately fixed in 95% alcohol and then interacted with the appropriate stain. The ratio of columnar to goblet cells in the normal nasal epithelium is 5:1. In an allergic response, the nasal columnar epithelial cells are replaced with Goblet cells resulting in a ratio of approximately goblet to columnar cells of 4:1. Eosinophils are the classic cells of allergy. They are frequently seen in the lamina propria but only rarely appear in the epithelium of normal individuals. Inhalant allergy is suggested if 20% or more of the granulocytes are eosinophils.

Skin Endpoint Titration

Skin endpoint titration is an intradermal skin test technique using 1:5 serial dilutions of allergenic extract. It can determine the endpoint of reaction to an inhalant allergen and the safe initial dosage for treatment of the detected allergies. The advantages of SET are safety, readability, standardization and safe for co-seasonal testing and treatment.

Skin tests are applied to the upper lateral arm at least 2 to 3 inches below the shoulder and 2 inches above the elbow. The intradermal injection of 0.01ml of any solution produces a wheal of approximately 4mm, which soon grows to about 5mm by spreading. Positive responses enlarge beyond this by the production of a “wheal and flare” response. For such a response to occur requires that skin mast cells have antigen specific IgE affixed to them. When the specific antigen bridges adjacent IgE units, chemical mediators such as histamine are released producing the Type I hypersensitivity. The wheal begins to grow within 2-5 minutes and maximizes in 10-15 minutes. Local vasodilation produces the accompanying flare response. Although the erythema should be noted in reading the skin test, only the diameter of the palpable induration at 10-15 minutes determines the reaction. If a hypersensitivity reaction is present, a positive wheal will enlarge at least an additional 2mm beyond the size of the negative 5mm wheal when a five fold progressively stronger concentration is used. The endpoint is defined as the antigen dilution that initiates progressive positive whealing. In other words, the dilution which yields a wheal at least 2mm larger than the preceding negative wheal, and which is followed by a wheal at the next stronger dilution that is at least 2mm larger. The second positive wheal is known as the “confirming wheal” and is important for determining the true endpoint.

Skin testing controls are a prerequisite for accuracy. Positive and negative controls are used to measure skin reactivity and to validate positive reactions. The negative control is the diluent used to make the testing dilutions. As mentioned above, the average mechanical change to a 0.01ml intradermal injection is a 4-5mm wheal. After 15 minutes, whealing responses larger than 5mm can indicate dermatographic skin. The next negative control should include the antigen preservative diluent which is commonly 2% glycerin (No. 2 glycerin), or 10% glycerin if testing of No.1 dilutions are anticipated. The glycerinated saline is commonly used because of its bacteriostatic properties and ability to stabilize the antigen for longer shelf life. The average skin response to 0.01ml of 2% glycerin is a 4-5mm wheal that grows to a 7-8mm wheal. If there is a positive reaction to the No. 2 glycerin indicates that endpoints on the No. 2 dilutions of various allergens are probably false-positive results. In Vitro testing may be used to confirm such a patient’s sensitivity. The No. 3 dilution of histamine is used as the positive control and determines the mast cell’s ability to release histamine. The average skin response to 0.01ml of No.3 Histamine is a 7-9mm wheal. Whealing larger than this can indicate dermatographic or hyper reactive skin. False negative results occur from medications, severe debilitating illnesses, or loss of antigen potency.

Abnormal whealing responses will occur in 5-15% of tests applied. The flash, hourglass, and plateau response are the most commonly encountered. The flash response is a huge whealing response of a very positive nature to a dilution that is weaker than the true endpoint. It is not a repeatable response and may often be eradicated immediately by applying weaker dilutions and moving forward through the flash to the true endpoint and confirming wheal. If the response can not be eradicated, then the test should be repeated 24 hours later. The plateau response is a 7mm or larger wheal that is followed by the same size wheal on progressively stronger dilutions until a dilution produces an additional increase in 2mm or larger. The dose that initiates the 2mm or larger wheal approximates the confirming wheal, and the preceding dilution approximates the endpoint dilution. The hourglass response is a large response of the initial weak dilution with progressively smaller reactions on stronger dilutions until a negative response occurs. It is then followed by a normal response. The initiation of the normal response

is the endpoint. This response is most frequently observed when testing begins at a very dilute level, usually weaker than a No. 6.

There are a variety of factors that influence skin test reactions. A wheal's initial size is directly related to the volume injected. The wheal size of a 0.01ml injection is approximately 4mm, whereas a 0.05ml injection creates a 7-9mm wheal. The reactivity of the sensitized skin mast cells and the degree of antigenicity of the solution injected affect the amount of histamine and other vasoactive amines liberated as a result of the skin test, and ultimately affect the resultant wheal. The skin of some individuals is overly responsive to trauma and a wheal and flare response will be seen in these patients even following the injection of an inert substance. Increased allergen exposure has the same effect on skin reactivity as the use of a stronger testing antigen. Therefore, patients will usually be found to be more sensitive to skin testing carried out during the season of their offending pollen. Concomitant food ingestion has been associated with the influence the whealing response. If this is suspected, testing in the semifasting state may be appropriate.

Antihistamines suppress the wheal and flare response. With most antihistamines on the market, the effect has ceased within 24 hours, and skin testing can be carried out 36 hours later. For shorter acting antihistamines, such as diphenhydramine, skin testing can be performed the next day. The histamine control will evaluate the integrity of the wheal and flare response. Tricyclic antidepressants can also suppress the response for 2-4 days. Patients who have undergone previous treatment may have altered skin test responses as compared to pretreatment levels due to the production of IgG blocking antibodies and lowered levels of allergen specific IgE.

Age is also important. It is rare to find an infant severely affected by inhalant allergy. Prior to the age of 3 years, the IgE necessary to elicit symptoms is limited. Thereafter, the IgE level increases in the sensitized patient, peaking in the 20's. The symptoms tend to follow the IgE level. There is normally a slow drop until middle age. There may even be a second peak in the 60's even though their reduced skin reactivity may make skin testing appear negative.

Allergens are generally divided into two categories as either seasonal or perennial. Pollens, trees, grasses and weeds are seasonal allergens. Perennial allergens are generally present year round and include house dust mite, molds and danders. In general, pollinating plants follow a predictable seasonal pattern. Trees pollinate in the spring, grasses pollinate in the summer and weeds pollinate in the fall with overlap being geographically related. A working knowledge of the local pollen guides cannot be emphasized enough. The pollens have a high degree of cross-sensitivity and certain representative grasses may be selected.

The most common pollen allergen is the short ragweed. Alternaria is the most important mold allergen, followed by Hormodendrum. Both should be commonly used. Other major allergenic molds include penicillium, cephalosporium, and aspergillus. The perennial allergens are not as numerous but offers the highest degree of relief with immunotherapy. The dermatophagoides, or house dust mite, are the most common perennial allergen. Cockroach allergens are important in urban areas. Dog and cat dander is common enough to be included in every panel.

Based on the results of the SET procedure, individualized treatments sets are custom designed for the specific patient. For those antigens that a patient has a high degree of sensitivity, weaker initial solutions are prepared; for those antigens with a low degree of sensitivity, stronger initial solutions are prepared. Separating low reactors (No. 1,2,3) from high reactors (no. 4,5,6) allows weaker dilutions to be escalated to more effective therapeutic ranges. If combined with stronger dilutions, such escalation may be blocked because of local or constitutional reactions. The strength of the weekly or biweekly injection is steadily increased to the point at which the patient has relief of symptoms or serious local reactions occur. The length of treatment is generally between 3-5 yrs, with significant improvement in clinical symptoms reached at approximately 4-6 months. The aim of this therapy is to induce a gradual change in the differentiation of T-Lymphocytes so that they preferentially become interleukin-2 and interferon gamma producing cells rather than Interleukin-4 synthesizing cells. These changes in the cytokine profile lead to a gradual reduction in IgE synthesis and inhibition of mast cell activation, thus impeding the release of the chemical mediators of immune inflammation.

In Vitro Testing

In Vitro tests eliminate variables associated with skin testing such as nonspecific whealing, effects of medications, and skin types. They are considered to be more specific but less sensitive than skin tests. Appropriate indications for use of in-vitro testing includes 1) impracticality of skin testing due to skin disorder, drug inhibition or uncooperative patients, 2) clarification of skin test results from bizarre or borderline results, 3) prevention of systemic reactions in patients with a prior history of or suspected anaphylactic reactions, asthma, or when testing for stinging hypersensitivity, and 4) convenience of in vitro testing.

The most common is the radioimmunosorbent assay (RAST). Allergen is coupled to a paper disc and incubated with the patient's serum. The disc is washed and radioactive IgE is added. After a second incubation, the disc is washed and a gamma counter quantitates the radioactivity. The modified RAST (MRT) involves an additional washing procedure in order to reduce non immunologically bound radioactivity. It has been shown to have an increased test sensitivity compared to RAST. The MRT scoring system is divided into five classes from 1-5, each representing approximately a fivefold increase in the amount of serum specific IgE antibody present in the sample. Before starting immunotherapy, it is mandatory to place an intradermal skin challenge of the initial vial. After the initial doses have been tolerated, injections can be escalated to therapeutic levels. The advantages of in-vitro tests include convenience for the patient, less time consumption, and lack of patient risk.

SNIT

Specific nasal immunotherapy (SNIT) applies the same principles as conventional immunotherapy while focusing more on recent knowledge to permit local treatment in individuals with limited allergic reactions. The World Health Organization now lists nasal immunotherapy as an alternative therapeutic option to the subcutaneous route. Although data is still somewhat limited, it appears to offer considerable advantages over other hypo sensitization methods.

Environmental control

The best treatment for inhaled allergens is avoidance of the inciting allergens. Complete avoidance is impossible, but minimizing contact should be a primary form of prevention. Animal danders can be effectively controlled. When faced with the choice, most patients are too attached to their pets to give them up. Cat dander can linger in carpet for up to 6 months after the cat is gone. If the animals can not be avoided, they must at least be kept out of the patient's primary living and sleeping areas. The most important antigen in house dust is the dust mite (*Dermatophagoides* spp). Application of commercially available Acarosol (benzyl benzoate) to carpets and upholstery can effectively remove the dust mites. High filtration air filters can be used in areas that the patient spends the most time, such as the sleeping quarters. Washing clothing and sheets in hot water and the use of special bedding can also prevent the accumulation of dander. Pollen avoidance is almost impossible short of giving up all outdoor activities, but pollen masks can be used when mowing or gardening. Avoidance of tobacco smoke and irritating fumes should be stressed.

Pharmacologic treatment

Pseudoephedrine is the most commonly used systemic decongestants. These drugs act by constricting vascular beds via alpha-adrenergic effects. Patient tolerance varies widely due to side effects of insomnia and irritability. With excessive doses, hypertension, nervousness, renal failure, cardiac arrhythmias, psychosis, strokes, and seizures can occur. The usual dose of pseudoephedrine is 15mg for children 2-4, 30mg for 6-12, and 60mg for adults every 6 hours.

Inhaled Cromolyn acts by inhibiting the degranulation of sensitized mast cells and therefore reduces the release of mediators that trigger inflammation and the allergic response. Cromolyn has been shown to inhibit both late and early phases of the allergic reaction. When used prophylactically it can prevent the onset of symptoms as well as treat nasal allergy symptoms once they occur. In addition to its effects on mast cells, it also inhibits macrophages, eosinophils, monocytes, and platelets believed to play a role in the inflammatory response. It is available as an OTC medication, supplied as a 4% solution in a nasal spray. The typical dosage is 1 spray per nostril 4 times daily. Its largest advantage is that it has very limited adverse effects. Cromolyn has not been associated with the reduced growth velocity that is associated with intranasal corticosteroids, therefore making it a good choice in children. The potency of cromolyn approaches that of antihistamines for some patients, but is less than that of topical steroids.

Antihistamines are currently the primary drug for treatment of nasal allergy. Antihistamines compete with histamine for H1 receptor sites on the target organs during the allergic response. They act prophylactically and are most effective when taken prior to allergen exposure. Most H1 antihistamines are also anticholinergic, antiserotonergic, and anti-alpha adrenergic. They are highly lipid soluble and readily cross the blood-brain barrier. Drowsiness and incoordination are common side effects. They are most effective at reducing symptoms such as sneezing, nasal itching, and rhinorrhea. Because they are less effective for nasal blockage, they frequently are combined with sympathomimetic drugs. The newer second generation antihistamines, such as loratadine, fexofenadine, cetirizine, and azelastine, are not necessarily more effective than first-generation antihistamines. They cross the blood brain

barrier less and have reduced CNS effects. In addition, there are no synergistic effects when taken with CNS depressants. The longer half life allows for up to once daily dosing.

Similar to histamine, leukotrienes are inflammatory mediators that contribute to the symptoms of the allergic response and are associated with vasodilation, increased vascular permeability, and mucus secretion in the lower airways. After nasal antigen challenge, cysteinyl leukotrienes may be among the most significant mediators of nasal congestion during the late phase response. By binding to leukotriene receptors on target cells, leukotriene receptor antagonists may block the effects of leukotrienes on congestion. However, the data available to date do not clearly support a unique role of leukotriene receptor antagonists in the treatment of allergic rhinitis.

Intranasal steroids are potent mediators of the inflammatory response. They primarily block the late phase reaction, but also block the early phase and reduce hyperresponsiveness. Only a small fraction of an intranasally administered drug is absorbed at the target site, although the major fraction is swallowed and undergoes gastrointestinal absorption. The newer intranasal corticosteroids, including budesonide, mometasone, and fluticasone undergo more complete first pass metabolism in the liver and have lower gastrointestinal absorption compared with the older corticosteroids. Epistaxis occurs in 5-8% of patients using any of these agents. Atrophy or thinning of the nasal tissue is also a concern with long term use. Clinical studies suggest that the newer corticosteroids have increased potency, reduced systemic availability and activity, quicker onset of action, and are at least as efficacious when compared to older corticosteroids. Consequently, they may be appropriate for replacing antihistamines as first line therapy for management of allergy as one meta-analysis showed that intranasal corticosteroids were significantly more effective than oral antihistamines at relieving all nasal symptoms including blockage, sneezing, itching, and discharge as well as at improving the total nasal symptom score.

Systemic steroids occasionally are used for patients with intractable rhinorrhea, total nasal obstruction, and greatly impaired sleep quality. A short course of daily oral steroids is an effective and low-risk approach. Intramuscular long acting depot steroid injections are also effective, but it is important to remember the cumulative adverse systemic effects that may result.

An additional means of delivering a glucocorticoid dose while minimizing systemic effects is by intratubinal injection of a repository form of a glucocorticoid. Concern over vasospasm or retrograde embolization of the retinal circulation causing blindness has caused this to lose popularity. However, when the proper technique is utilized, the procedure is now considered safe and effective. Intratubinal injection of 0.5ml of Triamcinolone acetate is carried out submucosally along the anterior tip of the inferior turbinate after topical decongestion. About 2% of patients may experience nasal bleeding or facial flushing. The facial flush is caused by steroid induced vasodilation and occurs the day following the injection. Injections are not repeated until symptoms return and are delayed at least 4-6 weeks after the last injection.

Pregnancy

Concerns for the fetus may confound treatment of pregnant patients with allergic rhinitis, since none of the medications used have been definitely proven to lack fetal effects.

Immunotherapy is judged to be safe if no systemic reactions develop. Because these reactions more commonly occur during initiation of treatment or during seasonal exposures, it should be avoided during these times. Astemizole and Cromolyn has not been associated with danger during pregnancy. Harm from topical steroids has not been proven, and are widely used during pregnancy.

Surgery

Surgery plays a minor role in the care of most patients with allergic rhinitis. Structural improvements in the airway may permit greater access for topical medications. Septoplasty and partial turbinate resections may benefit the nasal congestion for patients not responding to medical therapy. Whether cauterization, cryosurgery, or laser cautery of turbinates helps patients with allergic rhinitis by inducing submucosal fibrosis is unproved.

Allergic Emergencies

Adverse reactions following an injection of allergenic extract may be immediate or delayed. The delayed type reactions can be classified into local and systemic types and range on a spectrum from localized erythema and induration to pain and swelling significant enough to prevent arm motion. Delayed systemic reactions are generally seen as increases in the patient's usual allergic symptoms, but may also include generalized urticaria, and serum sickness like reactions. The inhalant antigens most likely to produce delayed reactions are the molds. The treatment is usually consists of administration of antihistamines and reassurance. Severe symptoms may necessitate systemic corticosteroids to prevent further late phase reactions.

Immediate reactions are type I reactions mediated by IgE. They are important because they are potentially fatal and require prompt recognition and management. The most common immediate reaction to an injection is a vasovagal one. The pulse rate is generally slow. A true anaphalactic reaction implies involvement of more than one organ system always involving the cardiovascular system. These patients will exhibit tachycardia in addition to wheezing, stridor and respiratory distress.

Initial management includes placing the patient in a supine position and loosening any constricting clothing. Establishment of an intravenous line is imperative. The mainstay of treatment is epinephrine (1:1000) given subcutaneously or intramuscularly in 0.3ml doses up to a maximum of 1ml. The injections should be given in the opposite arm. More anaphylactic fatalities result from airway obstruction than from cardiovascular collapse. Therefore oxygen and airway support should be readily at hand. Antihistamines, corticosteroids, and possibly H-2 blockers all will help reduce acute phase and late phase symptoms.

Patients who are receiving B-Blockers are at an increased risk for allergic reactions from all causes. The administration of epinephrine to the patients results in unopposed alpha adrenergic activity and may result in extreme hypertension. Tricyclic antidepressants and MAO inhibitors also potentiate the alpha adrenergic effects of epinephrine. Breakthrough doses of epinephrine should be avoided and dependence on other treatment modalities should be maximized.

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