TREATMENT OF MOLD ALLERGY USING INTRADERMAL TITRATION, RAST, AND SUBLINGUAL ANTIGENS

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Presented at:
AAOA Annual Meeting
Minneapolis, MN
September 30, 1993

Mold allergy is the most important and the most complicated inhalant allergy. There are very few controlled studies to indicate that injection therapy for molds works. The most recent study by Jean Bousquet was a carefully done double blind placebo controlled study using rush immuno-therapy with a standardized alternaria extract[1] . He could show efficacy when treating patients carefully selected that were only allergic to alternaria. He also used standardized extracts and predicted his final treatment dose by the initial skin testing. In the, Midwest USA, no patients seen in our clinic with 37 years' experience were only allergic to alternaria or any other single mold.

One previous positive study on injection immunotherapy by Ostergaard in Denmark was reported in 1986[2]. He was treating 26 children for mold allergy with large maintenance doses. Six patients developed severe anaphylaxis while on maintenance doses after some apparent tolerance had been achieved. Another study by Cantani in Italy in 1988 reported 39 children treated with mold injections to alternaria[3]. It was successful in 80% of the children given more than 80,000 PNU of alum precipitated alternaria. This is a very high dose, and I suspect many patients would never be able to achieve that high a dose.

One of the early reports of sublingual immunotherapy for molds goes back to 1970 when Morris reported success in sublingual antigen therapy in difficult mold cases including Farmer's Lung[4].

The presence of elevated IgE and IgG antibodies to alternaria in the Midwest USA was studied at our allergy clinic in La Crosse, Wisconsin. Antibodies to alternaria and aspergillus molds were measured in randomly selected allergy patients. Eighty-two had perennial nasal, and 101 had asthma. Forty patients used as controls were in a psychiatric unit and represented the immune reactions of the general population in a Western Wisconsin agricultural area. Antibodies were measured by RAST testing of the serum. Results were considered positive for IgE greater than 200% of negative control, and IgG greater than 12 ug/ml. The patients with asthma showed a high incidence of elevated IgE antibodies to both alternaria (33 of 101, 33%) and aspergillus (20 of 101, 20%) (Fig 1). IgG antibodies to alternaria were elevated in 13 of 101 (13%) (Fig 2), and IgG antibodies to aspergillus in 31 of 101 (31%). The patients with perennial nasal allergy showed IgE antibodies to alternaria (10 of 82, 12.2%) and aspergillus (3 of 82, 3.7%). They showed less

elevated IgG antibodies to alternaria (3 of 82, 3.7%), but a remarkable number were positive for IgG to aspergillus (30 of 82, 36.6%). In 40 controls representing the general population, some showed IgE antibodies to alternaria (3 of 40, 7.5%) and aspergillus (4 of 40, 10.0%). Some showed elevation of IgG antibodies to aspergillus (3 of 40, 7.5%) but none showed IgG antibodies to alternaria (0 of 40, 0%) (Fig 1 & 2). The elevated IgE antibodies would indicate the importance of molds in perennial nasal allergy and asthma. Since elevated IgG antibodies to molds are a probable contraindication to specific immunotherapy with maximum tolerated doses, it is important to test antibodies before beginning immunotherapy.

The relationship between aspergillus antigens and heat stress proteins may be why the IgG antibodies to aspergillus are so common even in those patients with nasal allergy. Even purified aspergillus fumigatus extract have recently been shown to be characterized by as many as 28 bands on immunoelectrophoresis[5]. It is interesting to note that some of the antigens in aspergillus are very similar to heat stress proteins. Heat stress (or heat shock) proteins are present in every cell type in our body. They are conserved during evolution of simple organisms and are important physiologic materials to help the organisms respond to stress. Major antigens of many bacteria (including mycobacteria, E Coli, etc.), molds (aspergillus, etc.), and candida yeast cross react because of this. These antigens provide a universal signal for infections and help our immune system respond quickly. They also, however, provide a link between infection and auto-immunity. Recently, there has been some interest in the rheumatology literature6. It is very likely that they are going to become very important in the field of allergy and immunology.

Testing of molds is of major importance in assessing the allergic patient. Testing for alternaria, cladosporium, aspergillus fumigatus, T.C.E. and mold A mixtures are the most important. The use of intradermal titration is the best and safest way to test these patients. It is important to test certain minor molds in specific cases, but with the complexity of antigens and the cross-reactivity of mold antigens, the major test molds are most important.

It is very important to ask patients to observe delayed reactions on the testing. Molds frequently cause extensive delayed reactions. Type 1 IgE reactions usually delay for 4 to 8 hours. Type 3 reactions delay for 8 to 24 hours, and Type 4 (cellular) responses delay for 48

to 72 hours. This must be considered in the early dosage of antigens. With molds that tend to delay strongly, it is important to start therapy at one or two dilutions below the end point.

Radioallergosorbent (RAST) testing can be very helpful in the diagnosis of mold allergy. We have seen in our study that IgE and IgG antibodies to alternaria and aspergillus are very common in patients with perennial nasal allergy and asthma. The RAST tests help to confirm and correlate with intelligent skin testing and history. It enables us to test the patient who is taking long acting antihistamines and helps us check on inappropriate skin reactions, be they positive or negative. The IgG antibodies are particularly important in immune complex diseases such as arthritis, urticaria, vasculitis, and candida hypersensitivity syndrome.

The use of sublingual antigens can be extremely safe, effective, and cost-effective. We utilize the immunologic principle of low zone tolerance. It is important to be sure to give the antigen frequently. Antigens are used for all inhalants three times daily at a cost of only $2.00 per week. Sublingual treatment has been criticized because it is given in doses which are too small. When one considers that an average drop of the antigen contains 1018 molecules (or a million trillion molecules), it takes on a different perspective. Peptides delivered with adjuvants cause stimulation, whereas antigens delivered without adjuvants may result in specific T-cell tolerance[7]. Soluble peptide can be used to induce tolerance to the peptide and to protein molecules containing that peptide. As we understand molecular biology, we realize that it only takes 300 molecules to tie up the T-cell receptors on a cell. If this is one of the mechanisms for low zone tolerance, each drop contains thousands of times more antigen than would completely make tolerant circulating T-cells.

The dosage of sublingual antigens are determined by the calculated amount for optimum dose immunotherapy. For single molds, this would be a 20 to 35x dose. For mold mixtures, it would increase to a 50x dose. This is the amount put in a 7.5 cc dropper bottle. Using it sublingually three times daily will treat for six weeks. As the patients end-points improve, the dosage of antigen is strengthened. When the patient is clinically doing well and the skin titrations improve, then treatment can be discontinued. In patients with severe contact with molds such as agricultural workers, the sublingual antigens must be continued as long as the patient gets strong exposures.

Recently, there has been a sublingual study which has been placebo controlled and failed to show effectiveness[8]. In the recent paper by Nelson et al., standardized cat extract was used only three times weekly sublingually. Twenty drops of antigen were used and were spit out after one minute. In low dose tolerance, the frequency of dose is extremely important, and the three times daily dose of titrated antigens would undoubtedly work better.

SUMMARY:

Mold allergy is the most important and complicated of inhalant allergies. Even purified single molds have many antigens. It is likely that recent evidence of cross-reaction with heat stress proteins may be a major factor in the immunologic importance of molds such as aspergillus and candida. Testing can best be performed by intraderm.al titration with observation of delayed reactions and with correlation by radioallergosorbent (RAST) testing of specific IgE and IgG antibodies to a few molds. Sublingual treatment is the safest and the most effective treatment for mold allergy.

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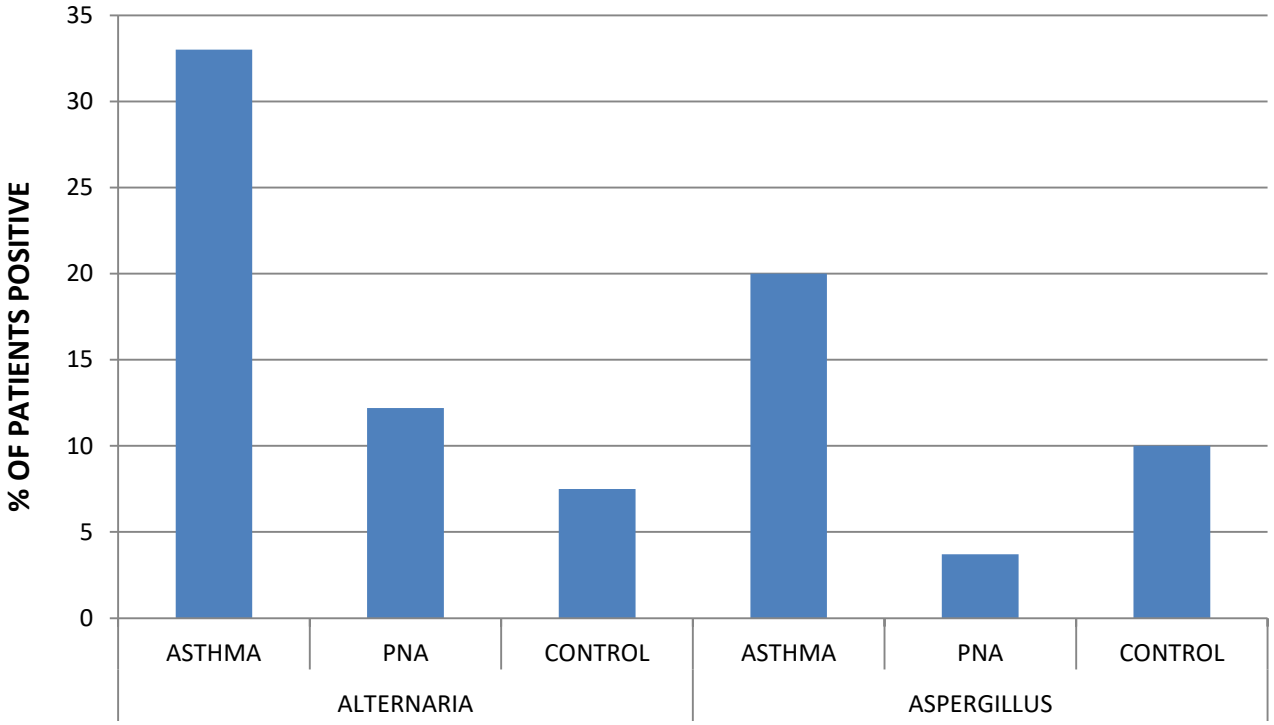
IGE AB TO ALTERNARIA ASPERGILLUS (Fig 1)



IGG AB TO ALTERNARIA ASPERGILLUS (Fig 2)