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Specific Immunotherapy in the U.S.A.: General Concept and Recent Initiatives

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Introduction

There are at least three factors that influence the allergy testing and immunotherapy practices in the U.S.: The U.S. allergic disease population, diagnostic and treatment practice parameters, and insurance reimbursement guidelines.

Estimates from a variety of sources suggest that allergies affect approximately 20% of the U.S. population or 56 million individuals (1-3). Not all allergic individuals seek physicians for primary treatment for their allergic disease and data are not readily available on the allergic disease patients that are candidates for allergen immunotherapy. However, recent data from Centers of Disease Control (C.D.C.) suggests that less than half of the allergic population seeks medical care for their allergic disease (4).

The Joint Task Force on Practice Parameters' recommendations to U.S. allergists guide the physician in selecting those patients for whom allergen immunotherapy is appropriate. Based on these recommendations, aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis and/or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens. Immunotherapy is also recommended for patients with a history of a systemic reaction to *Hymenoptera* stings and positive skin tests to *Hymenoptera* venom. Immunotherapy is not recommended for patients with food allergy, angioedema, or atopic dermatitis because of the lack of sufficient clinical studies. Additionally, sublingual, oral and intranasal routes for immunotherapy are considered as investigational.

Allergy testing and immunotherapy treatment is reimbursed through the medical claims reimbursement system. In these cases, most medical organizations cross-reference the International Classification of Diseases (ICD-9) and Current Procedural Terminology (CPT-4) coding systems to the medical necessity of allergy testing and/or

immunotherapy. These organizations adopt clinical and economic guidelines as the blueprints for access, medical necessity, and reimbursement. For example, reimbursement for allergen immunotherapy is normally restricted to patients with allergic rhinitis and/or asthma and *Hymenoptera* venom hypersensitivity.

There are a limited number of U.S. physicians and physician specialties that treat allergic diseases via allergen immunotherapy. A recent CPT-4 medical claims analysis (5) estimated 1.9 -2.7 million individual patients received allergen immunotherapy during 2001. Of the immunotherapy procedures, 3,400 allergists administered 78% of the procedures and 2,600 otolaryngologists administered 9%. Thus, approximately 3.3% of the 180,000 office-based physicians in the U.S. accounted for 87% of the reimbursed immunotherapy procedures in the U.S. Even among the limited number of physician specialists that practice immunotherapy there is a wide variation in immunotherapy prescription compounding and treatment approaches used. This variation is due in part to the variability of the allergic disease population and in part due to the diversity of therapeutic approaches taught at allergy training centers in the U.S. In addition, the standardization of immunotherapy practice is difficult when more than 95% of all immunotherapy prescriptions are compounded in more than 5,000 physicians' offices.

Recent U.S. Initiatives Affecting Immunotherapy Practices

The health insurance industry, physician medical associations and allergen product manufacturers are attempting to reduce unnecessary variation in immunotherapy practices. For example, The Centers for Medicare and Medicaid Services have revised payment policies for services and supplies incident to the administration of allergen immunotherapy. Specifically, the changes for CPT code 95165 (professional services for the supervision and provision of antigens for allergen immunotherapy) were recently adjusted to allow reimbursement only for the prescription maintenance concentrates and not for dilutions. In addition, the reimbursement value for allergen extracts used to compound a patient's prescription was based on the average cost using 6 allergens and a "dose" of 1.0 ml. Private insurance carriers have not yet adopted the ruling and it is difficult to assess its impact on current immunotherapy practices.

During 2000-2001 the majority of U.S. allergen product manufacturers received regulatory letters concerning precipitates in allergenic extracts based on findings during inspections made by the FDA. As part of corrective actions, commitments were made by the industry to [1] discontinue the shipment of precipitated products, [2] report precipitates as 'errors and accidents', [3] investigate the effect of precipitation on product potency and stability, and [4] modify current product labeling with a statement that precipitated extracts should not be used. Because many aqueous products tend to precipitate upon storage, these products were identified as unmarketable. Approximately 50 such products have been deleted from manufacturers' product catalogs in recent months.

The Joint Task Force for Practice Parameters, with members from the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), has been working on a revision of the

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Selected Summary Draft Immunotherapy

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Immunotherapy Practice Parameters. The draft guidelines (7), presented at recent AAAAI and ACAAI meetings, aimed to establish guidelines for the safe and effective use of allergen immunotherapy, while reducing unwanted and unneeded variation in immunotherapy practice.

Selected Summary Statements from the Draft Immunotherapy Practice Parameters (7)

**Standardized extracts/vaccines should be used whenever possible to prepare extract/
vaccine treatment sets.**

Extracts derived from cat hair, cat pelt, *D. pteronyssinus*, *D. farinae*, short ragweed pollen, grass pollen (Bermuda grass, Kentucky bluegrass, perennial ryegrass, orchard grass, Timothy grass, meadow fescue, red top, sweet vernal), and *Hymenoptera* venom (yellow jacket, paper wasp, honey bee, yellow hornet, white-faced hornet) are currently available in the U.S. as standardized products.

Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. The immunotherapy extract/vaccine should contain only clinically relevant allergens.

The omission of clinically relevant allergens from a prescription mixture may contribute to decreased effectiveness of allergen immunotherapy. The inclusion of all allergens to which IgE antibodies are present without establishing clinical relevance of these allergens can dilute the content of other allergens in the prescription mixture and make allergen immunotherapy less effective. Based on current evidence for optimal effective doses for allergen immunotherapy, the total number of products that can be added to a therapeutic mixture may be limited to approximately 10 components. This limit would vary depending upon the potency of stock allergen products used and the volume administered to the patient (see Table 2).

**The following principles should be considered when mixing allergen extract/vaccines:
a) cross-reactivity of allergens, b) optimizing dose amounts of each constituent, and c) enzymatic degradation of allergens.**

Knowledge of allergen cross-reactivity offers a practical advantage in the selection of allergens for immunotherapy and allows for fewer allergens in a treatment vial that helps in attaining optimal doses for the individual patient. When allergens from different sources are substantially cross-reactive, selection of a single extract within the cross-reactive group may suffice. In general, the patterns of cross-reactivities among pollens follow their taxonomic relationships (see Table 1).

The maintenance dose of allergen immunotherapy must be adequate and must be individualized for a particular patient. The prescribing allergist must balance the dose necessary to produce efficacy with the risk of a systemic reaction (see Table 2).

If mixing extracts causes excessive dilution or if mixtures include allergens with high proteolytic enzyme activities (esp. fungi and insects), separation of allergen extracts

into separate vials should be strongly considered. Glycerin at a concentration of 50% may inhibit the activity of proteolytic enzymes that are present in these extracts.

The highest concentration of an extract/vaccine that is projected to be used for the therapeutic effective dose is called the "maintenance concentrate".

A consistent and redundant labeling system for indicating dilutions from the maintenance concentrate may reduce errors in administration. The maintenance concentrate should be prescribed individually for each patient and appropriate documentation should be maintained for the production and administration schedule for each therapeutic mixture.

Table 1. Cross-reactive Pollens and Their Sources: Representative genera are members of the same botanical family or subfamily. Manufacturers currently offer allergen products derived from one or more species of each listed genus.

	Cross-reacting Groups	Representative Genera
Grasses	<i>Pooideae</i>	<i>Poa</i> (bluegrass), <i>Dactylis</i> (orchard), <i>Festuca</i> (fescue), <i>Lolium</i> (perennial rye), <i>Agrostis</i> (redtop), <i>Anthoxanthum</i> (vernal), <i>Phleum</i> (timothy)
Trees	<i>Aceraceae</i>	<i>Acer</i> (maples and box elder)
	<i>Betulaceae</i>	<i>Alnus</i> (alder), <i>Betula</i> (birches), <i>Corylus</i> (hazelnut)
	<i>Cupressaceae</i>	<i>Cupressus</i> (cypress), <i>Juniperus</i> (junipers and cedars), <i>Taxodium</i> (bald-cypress)
	<i>Fagaceae</i>	<i>Quercus</i> (oaks), <i>Fagus</i> (beech)
	<i>Juglandaceae</i>	<i>Carya</i> (hickory and pecan), <i>Juglans</i> (walnut)
	<i>Oleaceae</i>	<i>Olea</i> (olive), <i>Fraxinus</i> (ash), <i>Ligustrum</i> (privet)
	<i>Salicaceae</i>	<i>Populus</i> (cottonwood and poplars), <i>Salix</i> (willows)
"Weeds"	<i>Chenopodiaceae</i>	<i>Atriplex</i> (scales and saltbush), <i>Chenopodium</i> (lamb's quarter), <i>Salsola</i> (Russian thistle), <i>Kochia</i> (firebush).
	<i>Asteraceae:</i> <i>Artemisia</i>	<i>Artemisia</i> (mugworts, wormwood, and sages)
	<i>Asteraceae:</i> <i>Ambrosia</i>	<i>Ambrosia</i> (ragweeds), <i>Xanthium</i> (cocklebur)
	<i>Amaranthaceae</i>	<i>Amaranthus</i> (careless weed and pigweeds), <i>Acnida</i> (Western water hemp)

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Table 2. Effective therapeutic doses, and effective concentration of standardized and non-standardized extracts.

Allergen Extract	Labeled Potency	Effective Therapeutic Dose	Effective Therapeutic Concentration ¹
<i>Dermatophagoides</i>	5,000, 10,000 and 30,000 AU/mL	7-12 µg Der 1	1,000 – 4,000 AU/mL
Cat hair or Cat pelt	5,000 and 10,000 BAU/mL	11 – 17 µg Fel d 1	4,000 – 6,000 BAU/mL
Grass Pollen	10,000 – 100,000 BAU/mL	15 µg various	2,000 – 8,000 BAU/mL
Short Ragweed	1:10 – 1:20 w/v	6-24 µg Amb a 1	1:50 – 1:250 w/v
Hymenoptera Venoms	100 µg/mL	50-100 µg protein	100 µg/mL
Non-standardized Extracts	1:10 – 1:20 w/v	Maximum tolerable dose	1:50 – 1:250 w/v

¹assuming 0.5 mL per injection**Trends in Prescription Formulation Practices among U.S. Allergists**

The possible impact of these initiatives on formulation practices among U.S. allergists was evaluated by comparing the number of allergen components and the mean concentrations of standardized and non-standardized extracts in therapeutic mixtures produced during a typical production sequence at Greer Laboratories during 1999 and 2002 (see Table 3). A total of 582 allergen mixtures in 1999 and 1151 mixtures in 2002 prescribed by the same 20 allergists were examined. The data suggests that the allergists have reduced the number of allergen products in their patients' prescriptions. In

Table 3. Patient prescriptions formulated for U.S. allergists at Greer Laboratories.

	1999	2002
Mean Number of Component Extracts	10 (N=582)	8 (N=1151)
Mean Concentration of Standardized Grass Pollen Extracts	9171 BAU/mL (N=440)	8947 BAU/mL (N=732)
Mean Concentration of Cat Hair or Cat Pelt Extracts	1265 BAU/mL (N=102)	1365 BAU/mL (N=203)
Mean Concentration of Short Ragweed Extracts	1:222 w/v (N=128)	1:195 w/v (N=179)
Mean Concentration of <i>Dermatophagoides</i> Extracts	1157 AU/mL (N=299)	1083 AU/mL (N=500)
Mean Concentration of Non-standardized Extracts	1:292 w/v (N=546)	1:209 w/v (N=977)

the 1999 dataset, approximately 20% of the prescriptions contained more than 15 components and 6% contained more than 20 components in a mixture. In contrast, less than 3% of the prescriptions in the 2002 dataset contained more than 15 components. The average final concentrations of standardized allergen products (mite, cat, grass and short ragweed pollen) in the prescriptions were comparable for both years suggesting no significant changes for standardized extracts. However, the mean final concentrations of non-standardized allergen products in the prescriptions showed an increase from an average of 1:292 w/v in 1999 to 1:209 w/v in 2002. Inspection of the individual formulations revealed that both the increase in the mean concentrations of non-standardized allergen extracts and the reduction in the mean number of allergen components in an allergen mixture was due mainly to the exclusion of cross-reacting allergen extracts.

Conclusions

In the U.S.A., more than 95% of the 1.9-2.7 million therapeutic allergen mixtures produced each year are formulated by approximately 5,000 physicians' offices. Thus, uniform or standardized formulation practices have been difficult to implement. Some of these problems are being solved by continued focus by the manufacturers and regulators on the standardization of individual allergen products. In recent years, allergists in the U.S. are beginning to focus on special problems associated with product stability in mixtures, allergen cross-reactivity, and optimal dosing of allergens. Based on a limited survey of current practices, it appears that some progress is being made.

References

1. Gergen PJ, Turkeltaub PC, Kaovar MG. The prevalence of allergic skin reactivity to eight common allergens in the U.S. population: Results from the second National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 1987; 80: 669-679.
2. American Academy of Allergy, Asthma and Immunology. Task Force on Allergic Disorders. Executive Summary Report. 1998.
3. Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99: S808.
4. United States. Centers for Disease Control and Prevention. National Center for Health Statistics. Advance Data 195. 1996.
5. Greer Laboratories, Inc., The Empire Group, PharMetrics, Qunitiles Transnational Corp. January 2002.
6. Health Care Financing Administration. Rules and regulations. *Federal Register* 2000; 65: 65375-65424.
7. Joint Task Force on Practice Parameters (eds. Li JT, Lockey RF, Portnoy JM, Bernstein IL, Nicklas RA). Allergen Immunotherapy: A Practice Parameter (Draft). July 12, 2001.

Discussion

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Esch: Exactly. a therapeutic mix