

Skin Testing and Immunotherapy: Standardization in the Seattle Area

ASHLEY JERATH TATUM, M.D.

To my beloved mentor, colleague, and friend, Dr. Gail G. Shapiro.

ABSTRACT

Guidelines for the standardization of skin testing and subcutaneous allergen immunotherapy practice have been updated and published by the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology over the past 4 years. Goals of standardization include uniformity in the practice of skin testing and documentation, consistency in terminology used in allergen immunotherapy vaccine labeling, and improved efficacy of allergen immunotherapy vaccines. The allergen skin test form should include sufficient information for physicians other than the prescribing physician to understand what tests were performed, how they were performed, and how to correctly interpret results. Important factors to consider when formulating an immunotherapy vaccine include: crossreactivity of allergens, optimal dose of each constituent allergen, and possible enzymatic degradation of allergens by proteolytic enzymes. In an effort to adhere to published recommendations and to lead other allergists and communities toward standardization, board-certified allergists in the Seattle area have worked to increase the uniformity within the local practice of allergy skin testing and immunotherapy. National recommendations were presented and discussed at several meetings of the Paul P. Van Arsdel, Jr. Journal Club at the University of Washington in Seattle. These discussions focused on published recommendations, available evidence-based data, local and regional aerobiology, and individualized clinical practice. Standardized skin test forms were customized to include clinically relevant local aeroallergens, after examination of regional aerobiology and allergen crossreactivity patterns. Data presented during the meetings are summarized in this article, including 5-year (1998–2002) pollen counts collected during the spring in the Seattle area by Northwest Asthma and Allergy Center and therapeutic doses of major allergens to be included in an allergen immunotherapy vaccine maintenance concentrate. (*Pediatr Asthma Allergy Immunol* 2007; 20[3]:181–190.)

BACKGROUND

IN 2003, GUIDELINES FOR THE STANDARDIZATION of subcutaneous allergen immunotherapy practice were published by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology

University of Washington School of Medicine, and Northwest Asthma & Allergy Center, Seattle, Washington.

(ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI). These were recently updated, and working draft summaries were distributed at the 2007 AAAAI annual meeting in San Diego, California, (available on the JCAAI Web site www.jcaai.org).¹ Recommendations for the standardization of skin testing were developed by the Immunotherapy Committee of the AAAAI in 2003 (available on the AAAAI Web site www.aaaai.org). These guidelines provide allergists with a specific and uniform framework for the evaluation and treatment of patients. The recommendations were presented and discussed at several meetings, from 2003 to 2005, of the Paul P. Van Arsdel Jr. Journal Club at the University of Washington in Seattle in order to promote local and regional skin testing and immunotherapy standardization in step with the process of national standardization. These discussions focused on published recommendations, available evidence-based data, local and regional aerobiology, and individualized clinical practice. Data presented during the meetings are summarized in this article, and examples of locally adapted standardized skin test forms and immunotherapy practices adopted in the Seattle area are presented.

PURPOSE OF STANDARDIZATION

The goals of standardization include: (1) uniformity in the practice of skin testing and documentation; (2) consistency in terminology used in allergen immunotherapy vaccine labeling; and (3) improved efficacy of allergen immunotherapy vaccines and documentation of vaccine content. Standardization provides clarity of diagnostic and therapeutic information for both physicians and patients, and allows for precise data reproducibility and simple portability of medical information. The objective is to improve the quality of the practice of skin testing and allergen immunotherapy for patients while reducing unneeded variation within clinical practices. When patients transfer care from one physician to another, the new physician should be able to easily and accurately interpret data collected by other providers and understand fully the nature of allergen immunotherapy vaccine constituents in order to duplicate the vaccine if needed.¹ Minimizing variability across the specialty of clinical allergy strengthens the specialty within medicine and enhances allergists' ability to deliver optimal care to their patients. To advance this objective, the Immunotherapy Committee of the AAAAI developed template forms for the documentation of skin testing and immunotherapy vaccine contents that can be downloaded from the AAAAI Web site. The purpose of these forms is to provide a uniform format for documentation within which local, regional, and individual customization can be considered.

STANDARDIZED DOCUMENTATION FOR SKIN TESTING

Immediate-type skin testing has been the primary diagnostic tool in clinical studies of allergen immunotherapy. Therefore, in most patients skin testing is used to determine the presence of aeroallergen specific IgE. Among the skin testing techniques available, a properly applied percutaneous test (prick) and intracutaneous (intradermal) test using a nonirritating concentration of allergen extract (less than 1:100 weight per volume) may be conducted.¹

The allergen skin test form should include sufficient information for physicians other than the prescribing physician to understand what tests were performed, how they were performed, and how to correctly interpret results. Standardized forms provided by the Immunotherapy Committee of the AAAAI provide the framework for the inclusion of the following essential information: (1) patient information, including patient name and date of birth; (2) ordering physician information, including physician name, address, and phone number; (3) date of skin test; (4) date of the last administration of medications that can interfere with skin test reactions (e.g., antihistamines, antidepressants); and (5) skin test methods, including skin test technician, location of test (e.g., back or arm), type of test (e.g., prick, intradermal), instrument used for testing (e.g., name of testing device, needle size, commercial kit), amount of allergen extract injected for intradermal tests, and time elapsed between application and reading of tests. Documentation of testing materials used should include allergen name (including pos-

itive and negative controls), manufacturer or source of allergen extract, and allergen extract concentration. Results are most accurate when the longest diameter of the wheal and erythema/flare size is measured and reported in millimeters.¹ The quantitative method of reporting skin test results can improve accuracy, precision, and uniformity of allergy testing and interpretation. Also helpful is the in-

FIG. 1. Blank standardized skin test form. Developed by the AAAAI Immunotherapy Committee, 2002. Available from the AAAAI website: www.aaaai.org.

TATUM

clusion of the prescribing physician's interpretation (e.g., positive, negative, or equivocal) of skin test results. A blank skin test form available on the AAAAI website and a modified skin test form customized to include relevant aeroallergens in the Seattle area are provided in Figures 1 and 2, respectively.

Northwest Asthma & Allergy Center, P.S. 4540 Sand Point Way NE Seattle, WA 98105-3941 206-527-1200 1801 E. Division Mt. Vernon, WA 98274 360-424-4410 108 Columbia Point Dr., Suite E Richland, WA 99352 509-946-0189 1819 100th PL. SE, Suite B Everett, WA 98208 425-385-2802 3901 Creekside Loop, #100 Yakima, WA 98902 509-966-3259 8301 161st Ave. NE, Suite 208 Redmond, WA 98052 425-885-0261 1412 SW 43rd St., #210 Renton, WA 98055 425-235-1716																																																																																																																																																																																																																																																																																																																																																													
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FIG. 2. Customized skin test form.

Allergen selection

It is recommended that physicians select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area. The clinical relevance of pollen allergens is based on the following properties: (1) intrinsic allergenicity; (2) aerodynamic properties and sufficient bouyancy allowing long - distance travel; and (3) abundance of a pollen-releasing plant in a region. Major clinically relevant aeroallergens in North America have been identified by the AAAAI Immunotherapy Committee and Allergen subcommittee.¹ Using this information along with regional data collected by manufacturers of allergen extracts, local pollen counts collected by Northwest Asthma and Allergy Center in Seattle, and information gathered from local urban and state forestry departments, clinically important aeroallergens were identified for use in skin testing in the Seattle area (Table 1). These include allergenic proteins from dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat pelt, dog hair-dander, molds (*Alternaria*, *Cladosporium*, *Penicillium*, *Aspergillus*, and *Helminthosporium* species), and pollens from representative trees, temperate grasses, and weeds. Cockroach allergen extract is not often used, as cockroach specific IgE is not commonly found via *in vivo* testing in local patients. Specific IgE for German cockroach was found in 11% (41/ 366) of allergic patients randomly sampled at Northwest Asthma and Allergy Center (unpublished data). Five-year (1998–2002) data representing pollen counts collected during the spring pollinating seasons in the Seattle area is illustrated in Figures 3–5. Pollen was collected using a Rotorod sampler (rotation of 60 seconds every 10 minutes). Calculated points are a monthly average of pollen counts for each tree allergen over a 5-year observational period.

Knowledge of allergen crossreactivity patterns is used to limit the number of skin tests conducted and the number of allergens placed in an immunotherapy vaccine. Alder, birch, hazelnut, and walnut trees are prevalent in the Pacific Northwest and exhibit extensive crossallergenicity. Based on the consensus opinion of local allergists, use of alder and birch for testing, and one or both for treatment (accounting for cross-reactivity) is appropriate. Of the evergreen trees, the most clinically relevant allergens are those from juniper, cedar, and cypress (less important in the Pacific Northwest) trees. Pollen from juniper and cedar trees

TABLE 1. MAJOR CLINICALLY RELEVANT AEROALLERGENS IN THE SEATTLE AREA

Tree pollen
Red Alder (<i>Alnus rubra</i>)
Paper birch (<i>Betula papyrifera</i>)
Cottonwood (<i>Populus trichocarpa</i>) and poplar (<i>Populus nigra</i>)
Western juniper (<i>Juniperus occidentalis</i>) and Red cedar (<i>Juniperus virginiana</i>)
Coast maple (<i>Acer macrophyllum</i>)
Red oak (<i>Quercus rubra</i>)
Oregon Ash (<i>Fraxinus latifolia</i>)
American elm (<i>Ulmus americana</i>)
Grass pollen
Pasture grasses (e.g., timothy, orchard, perennial rye)
Weed pollen
English plantain (<i>Plantago lanceolata</i>)
Lambs quarters (<i>Chenopodium album</i>)
Yellow dock (<i>Rumex crispus</i>)
Indoor aeroallergens
Cat pelt (<i>Felis domesticus</i>)
Dog hair—dander (<i>Canis familiaris</i>)
Dust mites (<i>D. farinae</i> , <i>D. pteronyssinus</i>)
Fungi
<i>Alternaria</i> species
<i>Aspergillus</i> species
<i>Penicillium</i> species
<i>Helminthosporium</i> species
<i>Cladosporium</i> species

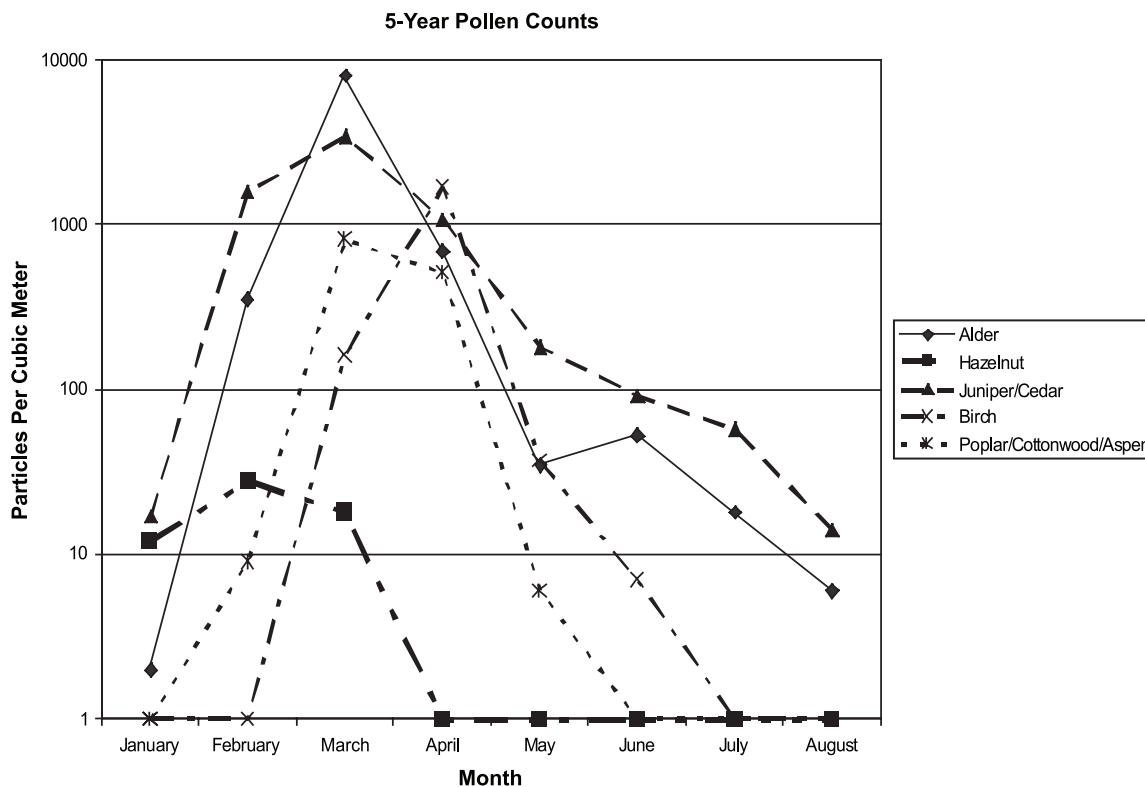


FIG. 3. Seattle area monthly pollen counts: alder, hazelnut, juniper/cedar, birch, poplar/cottonwood/aspen trees. Data is presented as a 24-hour average of particles per cubic meter of air. Each pollen graph is presented using a logarithmic scale.

strongly crossreacts, and thus inclusion of one allergen for testing and treatment is sufficient. Likewise, cottonwood, poplar, and willow pollens are crossreactive and pollen counts peak at the same time; thus, use of a single pollen (or commercially available cottonwood–poplar extract mix) is adequate. Pollens from local elm, oak, ash, and maple trees each contain unique and important allergenic epitopes.¹ According to data gathered from local urban and state forestry departments, the plantings of elm and ash trees have recently increased, whereas the plantings of walnut trees have decreased in Seattle. Maple, ash, and oak trees are among the most common trees lining Seattle city streets. Red alder, maple, cottonwood, willow, oak, fir, and pine trees make up much of the native material in city greenbelts and in forested areas surrounding Seattle. Temperate pasture grasses (e.g., fescue, rye, timothy, orchard, red top) contain major allergens with significant crossreactivity; however, timothy also possesses unique allergens, which are important locally. Thus, use of timothy and one other pasture grass is practical. Clinically important and unique weed allergens in Western Washington include English plantain, lambs quarters, and yellow dock. In Eastern Washington, important weeds include kochia, russian thistle, sagebrush (cross-reactive with mugwort), and ragweed. *D. pteronyssinus* and *D. farinae* contain both unique epitopes and those which are strongly crossreactive; thus, both are considered individually for testing and treatment (with appropriate dose modification).¹

STANDARDIZED PRESCRIPTIONS FOR ALLERGEN IMMUNOTHERAPY

Nomenclature

Standardized nomenclature in labeling allergen immunotherapy vaccine vials as recommended by the Joint Task Force on Practice Parameters was discussed and implemented by board-certified allergists in

SKIN TESTING AND IMMUNOTHERAPY

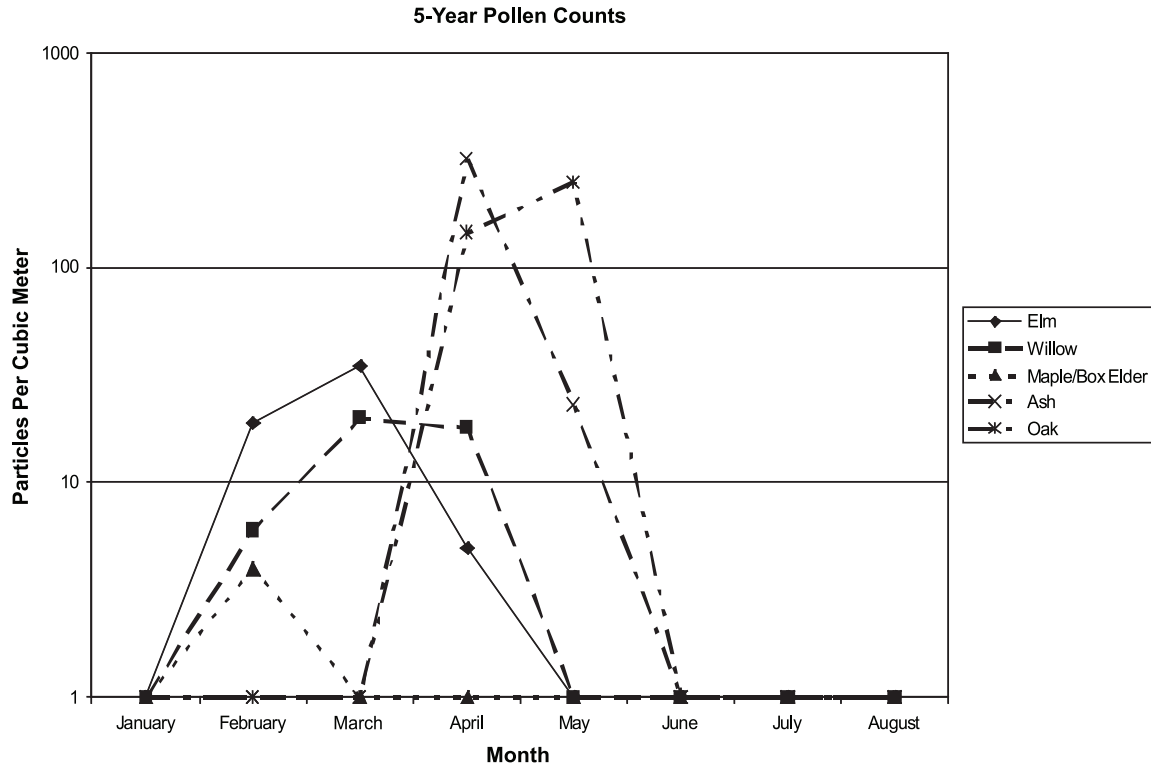


FIG. 4. Seattle area monthly pollen counts: elm, willow, maple, ash, and oak trees. Data is presented as a 24-hour average of particles per cubic meter of air. Each pollen graph is presented using a logarithmic scale.

the Seattle area. A consistent and redundant labeling system for immunotherapy vaccine vials can increase patient safety when transferring care including administration of immunotherapy to another physician. Uniformity in vaccine vial nomenclature can reduce errors by the office of the new physician in administration of injections from the appropriate vial. The highest concentration of an immunotherapy vaccine that is estimated to contain a therapeutically effective dose, individualized for each patient, is called the maintenance concentrate. The maintenance concentrate should contain therapeutically effective doses for each of its constituent components. Serial dilutions of the maintenance concentrate are prepared for use in the build-up phase of immunotherapy. In order to indicate that they are dilutions derived from the maintenance concentrate, standardization nomenclature arranges these dilutions in terms of volume to volume (v/v). For example, the maintenance concentrate is labeled 1:1 v/v, a 10-fold dilution is labeled 1:10 v/v, a 100-fold dilution is labeled 1:100 v/v, a 1,000-fold dilution is labeled 1:1,000 v/v, and a 10,000-fold dilution is labeled 1:10,000 v/v. Additionally, use of a universally accepted color-coding system is helpful. The recommended color-coding system is as follows: the most concentrated vaccine should be labeled red, the next most concentrated yellow, followed by blue, green, and silver in proper order.¹

Immunotherapy vaccine constituents: effective concentration and mixing

An immunotherapy vaccine should contain appropriate allergen extracts on the basis of a patient's clinical history, allergen exposure, and skin testing data. Whenever possible, standardized allergen extracts are used to prepare the vaccine. The following factors are considered when formulating an immunotherapy vaccine: (1) crossreactivity of allergens, (2) optimal dose of each constituent allergen, and (3) possible enzymatic degradation of allergens by proteolytic enzymes. When one allergen elicits the same response as another, only one of the crossreacting allergens is included in an immunotherapy vaccine; otherwise, a patient

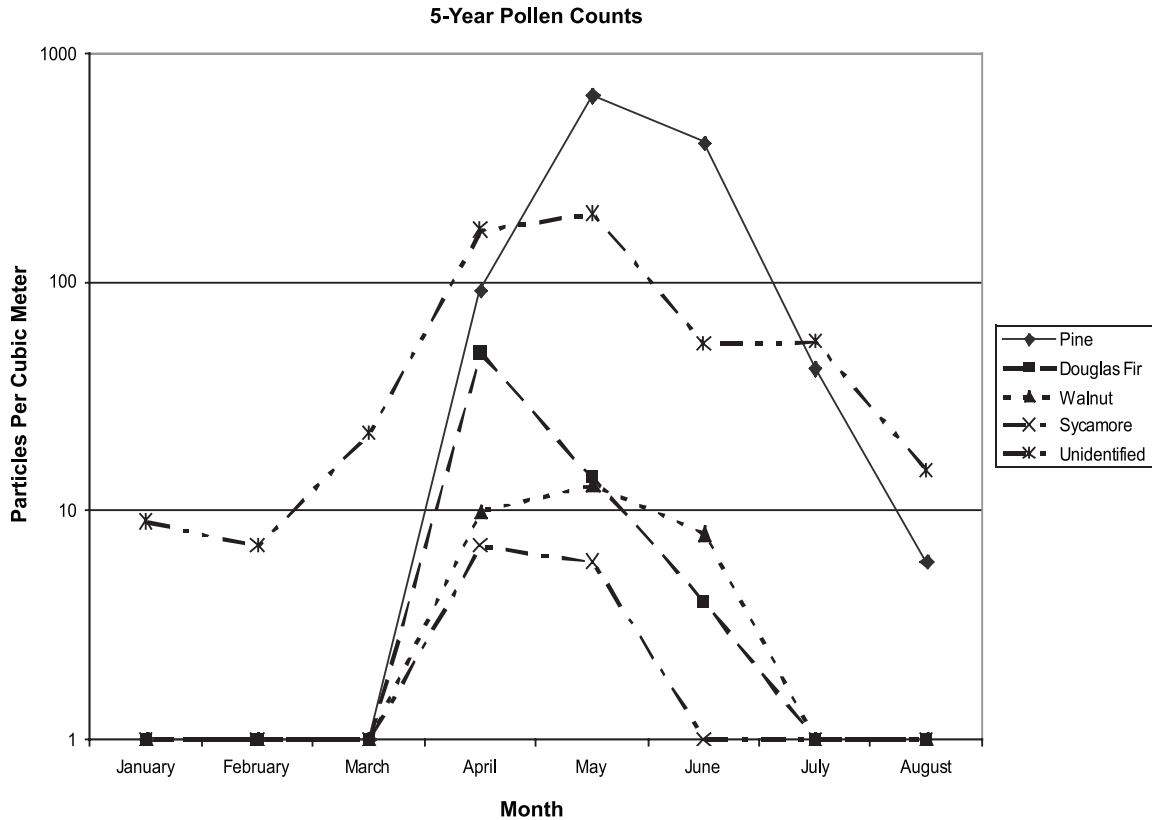


FIG. 5. Seattle area monthly pollen counts: pine, fir, walnut, and sycamore trees. Data is presented as a 24-hour average of particles per cubic meter of air. Each pollen graph is presented using a logarithmic scale.

may receive a higher than desirable allergen dose. Also, too many allergens within a vaccine vial can result in unnecessary dilution of constituent allergens and reduced vaccine efficacy. For patients allergic to both *D. farinae* and *D. pteronyssinus*, only 50% of the projected amounts of each house dust mite allergen may be included in an immunotherapy vaccine due to the significant crossreactivity between their major allergens. In general, allergen extracts that have high proteolytic enzyme activity, such as those originating from fungi, are kept separate from those with lesser enzymatic activity, such as pollens (see Table 2).¹

TABLE 2. AEROALLERGENS COMPATIBLE FOR MIXING TOGETHER

<i>High protease activity</i>	<i>Low protease activity</i>
Dust mites ^a	Grass pollens
Fungi	Tree pollens
Cockroach	Weed pollens ^b
	Animal dander

Based on recommendations of the Joint Task Force¹ and local consensus.

^aDust mite: Glycerin can inhibit proteolytic enzymes in dust mite bodies (allergen extracts available in the United States); thus, dust mite allergen can be mixed with allergens containing low protease activity as well.

^bRagweed allergen may be mixed with either group above.

SKIN TESTING AND IMMUNOTHERAPY

TABLE 3. RECOMMENDED EFFECTIVE DOSES OF ALLERGENS IN MAINTENANCE CONCENTRATE

<i>Allergen</i>	<i>Manufacturer's concentration</i>	<i>Effective concentration</i>	<i>Dose, major allergen</i>
Dust mites:			
<i>D. farinae</i>	10,000 AU/ mL	2,000–4,000 AU/mL	10ug Der f 1 ²
<i>D. pteronyssinus</i>	10,000 AU/ mL	1,200–2,400 AU/mL	7–12 ug Der p 1 ²⁻⁴
Cat	10,000 BAU/ mL	4,000 BAU/mL	11–17 ug Fel d 1 ⁵⁻⁸
Grass (pasture grass)	100,000 BAU/ mL	6,000–8,000 BAU/mL	7–15 ug1, 9, 10
Non-standardized pollen/mold	1:10 w/v	1:200–1:100 w/v	N/A
Non-standardized pollen/mold	1:20 w/v	1:200–1:100 w/v	N/A
Dog	AP 1:100 w/v*	—	15ug Can f 1 ¹¹

Adapted from Joint Task Force recommendations¹ and local allergist consensus opinion. Doses of allergens are based on a planned 0.5 mL injection of maintenance concentrate. Appropriate dose reduction advised when using allergens with strong cross-reactivity.

*Acetone-precipitated.

Therapeutic doses of major allergens to be included in the maintenance concentrate range between 5 and 20 μ g. Recommended effective concentrations of standardized and nonstandardized allergens are listed in Table 3. The volume of manufacturer's allergen extract to add to an immunotherapy vaccine to achieve a therapeutic concentration can be calculated by dividing the projected effective concentration of allergen by the concentration of available manufacturer's extract times the total volume (e.g., Cat: 4000 BAU [effective concentration for a 0.5 mL injection] divided by 10,000 BAU [manufacturer's extract concentration] $\times$ 5 mL [total volume of vaccine vial] = 2 mL [amount allergen extract needed in 5 mL vaccine vial]). For nonstandardized extracts, usually 0.5 mL of a 1:100 weight per volume dilution of manufacturer's allergen extract is added, assuming a 0.5 mL injection of maintenance concentrate is delivered.¹

SUMMARY

Standardization provides clarity of diagnostic and therapeutic information for both physicians and patients. In an effort to adhere to published recommendations and to lead other allergists and communities toward standardization, board-certified allergists in the Seattle area have worked to increase uniformity regarding the local practice and documentation of allergy skin testing and immunotherapy. Standardized skin test forms were customized to include clinically relevant local aeroallergens, after examination of regional aerobiology and allergen crossreactivity patterns. Use of the quantitative method of measuring and reporting skin test results was adopted to increase testing accuracy and reproducibility. Consensus agreement was achieved regarding effective concentrations of allergens within immunotherapy vaccines. Use of consistent terminology in labeling immunotherapy vaccine vials and formulation of therapeutically effective maintenance concentrates has been implemented to increase the general safety and efficacy of allergen immunotherapy. Broad-based implementation of published guidelines regarding skin testing and immunotherapy standardization can ultimately improve the quality of patient care and advance the specialty of allergy.

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