ALLERGENIC EXTRACTS USED IN THE TESTING AND TREATMENT OF ANIMAL ALLERGIES

POLLENS, MOLDS, DUSTS, INHALANTS, EPIDERMALS, FOODS AND INSECTS

DESCRIPTION

Pollens

Pure dry pollens are defatted in ether and extracted in an aqueous buffered dilution. Grass pollen, which is a common cause of atopy, is more prevalent in late spring and early summer. Weeds are prolific producers of pollen and can cause animal allergies, especially in the late summer and early fall. Tree pollens can also cause allergies, although the pollination season for each species is relatively short.

Fungi

Extracts of fungal allergens are derived from the mycelia and spores of pure culture fungi (molds) including yeasts or from the basidiospores of rusts and smuts, collected from their natural environments. The extracts of fungi are prepared from defatted fungal material extracted in an aqueous buffered solution. Airborne fungi are an important cause of animal allergies and can be present indoors throughout the year. Outdoors, fungi can also be found in large numbers from May to December, with peak periods varying according to specific fungi and climate conditions.

Dusts

Dusts are extracted in an aqueous buffered solution and dialyzed to remove non allergenic irritants. House dust extract is concentrated to achieve the labeled Protein Nitrogen Units per milliliter (PNU/mL). House dust is a common cause of atopy due to its heterogeneous composition and presence in the home.

Epidermals, Miscellaneous Inhalants, and Foods

Epidermal extracts are made from hide, hair, or feathers and contain natural danders. Miscellaneous inhalants and most food extracts are prepared using defatted materials obtained from, unprocessed natural source of the inhalant or edible food when possible.

A small group of foods, primarily cereal grains, are extracted with fluid containing 0.1% sodium formaldehyde sulfoxylate (SFS), an antioxidant. This results in a light-colored extract that minimizes the potential tattooing effect that can occur after skin testing with oxidized extracts. Extracts containing SFS are labeled "For Diagnostic Use Only."

Insects

Insect extracts are made from the whole bodies of insects collected from their natural habitats or that are grown in laboratory colonies.

Preservatives

Aqueous extracts contain 0.4% phenol as an antimicrobial preservative. Extracts may also be supplied in 50% glycerin. Extracts diluted with 50% glycerin containing 0.2% phenol provide allergenic stability and antimicrobial attributes.

MECHANISM OF ACTION

The interactions of allergens with mast cell bound specific immunoglobulin E (IgE) stimulates the release of mediators such as histamine. These mediators can induce mechanisms that cause induration (wheal) and erythema at the site of skin testing along with other allergic signs. These correlate to the level of hypersensitivity to the specific allergen. Skin testing is an aid to confirm the diagnosis of atopy. Allergy immunotherapy generally results in a modification to the cellular regulatory mechanisms involved in the allergenic reaction causing an increase in allergen specific immunoglobulin G (IgG) antibodies. These antibodies have been postulated to block the circulating allergen before it can bind to the IgE present in the tissues and trigger an allergic response.[1] Clinical improvement, however, does not necessarily correlate well with increased levels of IgG antibodies, and IgG levels vary during long-term therapy. Additional mechanisms may be involved in the relief of signs upon continued administration of allergy immunotherapy.

INDICATIONS

1. **DIAGNOSTIC:** GREER allergenic extracts are useful aids in the skin test diagnosis of allergies. Clinical signs and history are also necessary to establish the diagnosis.

2. **THERAPEUTIC:** GREER allergenic extracts are indicated for allergy immunotherapy (hyposensitization) to aid in alleviating signs associated with atopy. Avoidance or reducing exposure to the offending allergen, if possible, should be initiated prior to or concurrently with allergy immunotherapy. Concomitant antibiotic therapy and an appropriate bathing program should be instituted where significant secondary bacterial infection of the skin is evident. Short-term corticosteroid therapy may be used as an additional treatment in early stages of therapy. Food extracts are not recommended for use in allergy immunotherapy but may be useful for diagnosis.

CONTRAINDICATIONS

1. **DIAGNOSTIC:** Skin testing is contraindicated in patients on corticosteroids or drugs with antihistamine activity that can cause inhibition of the histamine-mediated skin test reaction. These drugs should be withdrawn for a period sufficient to allow the patient to exhibit a positive skin test response to histamine control. The withdrawal time for antihistamines is based on their biological half-life. The withdrawal time for corticosteroids is about one week for each month of continual corticosteroid administration. Patients with inflamed or infected skin should not be skin tested until appropriately treated and their skin condition improves.

2. **THERAPEUTIC:** Because the patient may have a non-IgE-mediated sensitivity, allergens are not indicated for hyposensitization immunotherapy unless specific allergen hypersensitivity has been identified by means of intradermal skin testing, or in vitro allergen-specific serum IgE testing, and confirmed by clinical signs, history, and differential diagnosis to rule out other etiologic conditions.

PRECAUTIONS

For percutaneous, intradermal, subcutaneous or sublingual-oral use only.

Have the following available:

- Epinephrine hydrochloride injection (1:1,000 dilution).
- Fast-acting, water-soluble corticosteroid injection such as hydrocortisone, prednisolone, or dexamethasone.
- Injectable antihistamine such as diphenhydramine.

Keep the patient under observation for at least 30 minutes after administration of testing or treatment. Patients prone to severe reactions should be given diphenhydramine or another appropriate antihistamine 30 minutes prior to treatment administration.

Extracts in 50% glycerin should be diluted with an aqueous diluent before subcutaneous or intradermal use to avoid discomfort due to the high concentration of glycerin.

ADVERSE REACTIONS

Adverse reactions are very rarely seen and usually consist of an exacerbation of clinical signs if too large a dose is given. If the patient is highly sensitive or an overdose occurs signs may include: restlessness, panting, generalized hives, vomiting, circulatory collapse, and/or diarrhea.[2] Additionally, following sublingual-oral allergy immunotherapy administration, adverse reactions may include: facial edema, erythema, pruritus, oral paresthesia, diarrhea, and sneezing (see **OVERDOSAGE** for treatment).

Temporary pain and discomfort may be experienced at the time of injection, with some stiffness and soreness occurring later. A small area of ulceration can occur at the injection site following intradermal administration.

OVERDOSAGE

If signs of overdosage occur (see **ADVERSE REACTIONS**) one or more of the following can be effective for treatment:

- Immediate intramuscular injection of 0.01 mL/kg (per kg of body weight) epinephrine in a 1:1,000 dilution, or in the case of a severe reaction, administer a 1:10,000 dilution intravenously in increments of 0.5 mL to 1.0 mL to a total dosage of 0.5 to 5.0 mL. Epinephrine administration can be repeated every 15 to 30 minutes as needed.
- Intravenous injection of an appropriate corticosteroid such as 35 mg/kg of prednisolone sodium succinate, or dexamethasone sodium phosphate 5 to 10 mg/kg.
- Slow intravenous infusion of an antihistamine such as 1 to 2 mg/kg of diphenhydramine hydrochloride.

INTRADERMAL SKIN TESTING - DOSAGE AND ROUTE OF ADMINISTRATION

The signs of atopy may be seasonal or perennial depending on the patient's sensitivities. Selection of the appropriate seasonal allergens for testing should be based on the geographical region where the patient resides. When a perennial allergy is suspected, allergens such as house dust, mites, and molds should be included for testing. If unrelated allergenic extracts are combined, specific allergens can be masked or diluted by others in the mix. This can lead to a false negative result. A positive result when using a mix does not permit discrimination making it difficult to determine the patient's specific allergen sensitivities. Although food extracts can be helpful in confirming or ruling out suspected food allergies, they are not recommended for use in a definitive diagnosis. Elimination diets remain the best method for diagnosis of food allergies. Positive intradermal skin tests or other allergen-specific test results should be evaluated along with clinical signs and patient history before the course of treatment is selected.

Intradermal Skin Testing

1. Materials Needed

- Sterile 1 mL tuberculin type syringes with ⅜ to ½ inch, 26 or 27 gauge needles.
- Negative control (saline diluent).
- Positive control: The available Histamine Phosphate, 0.275 mg/mL, should be diluted 1:10 to yield 0.0275 mg/mL.
- Allergens at 1,000 PNU/mL or 1:1,000 w/v (final concentration).

The following allergens may give more consistent results when tested at concentrations lower than 1,000 PNU/mL or 1:1,000 w/v:

GREER Item #	Product Name	Strength
149	Corn, Cultivated (*Zea mays*)	250 PNU/mL
BO4	4 Insect Mix (American Cockroach, House Fly, Moth, Mosquito)	250 PNU/mL
M23	*Rhizopus nigricans* (*Rhizopus stolonifer*)	100 PNU/mL

GREER Item #	Product Name	Strength
MO12	*Rhizopus* Mix (*R. arrhizus*, *R. nigricans*)	100 PNU/mL
MO2	Mold Mix #2 (*Curvularia specifera*, *Fusarium moniliforme*, *Mucor plumbeus*, *Pullularia pullulans*, *Rhizopus nigricans*)	250 PNU/mL
D9	House Dust	100 PNU/mL
DO1	HMRU Dust Mix (House, Mattress, Rug, Upholstery)	100 PNU/mL
E27	Sheep Epithelia (*Ovis aries*)	500 PNU/mL
H7	Silk (*Bombyx mori*)	500 PNU/mL
B51	House Dust Mite *Dermatophagoides farinae*	1:1,000 to 1:50,000 w/v
B58	House Dust Mite *Dermatophagoides pteronyssinus*	1:1,000 to 1:50,000 w/v
BO60	Mite Mix, Equal Parts Mixture (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)	1:1,000 to 1:50,000 w/v

2. Suggested Procedure

Before testing, the patient may be sedated. Care must be taken to avoid sedatives with antihistamine activity such as acetylpromazine. Xylazine may be used.

a. Prepare the test area (usually the lateral thorax) by clipping fur/hair and gently cleaning the test site with a moist towel if necessary. Skin that is inflamed or infected should not be tested. Sites may be marked for easy reading.
b. Using a separate syringe for each solution, load syringes with a minimum of 0.1 mL for negative and positive control solutions and the test allergen extracts.
c. The injection sites should be at least 2.5 cm from each other.
d. Gently stretch the skin and insert the needle at an approximate 10-degree angle with the bevel facing upwards.
e. Once the entire bevel is buried in the skin, inject 0.05 mL each of the positive and negative control solutions and each allergenic extract forming a bleb in the skin at separate test sites.
f. The skin test should be completed for all allergens as soon as possible to allow for comparison against the controls.

3. Interpretation of Skin Test Results

a. Read skin test results 15 minutes after injection. The wheals are best observed by oblique or side lighting in a darkened room. Immediate (IgE mediated) reactivity will cause a wheal within 15 minutes. Reactions may occasionally be seen after 24 to 48 hours.
b. A wheal diameter that is significantly greater than the negative control indicates a positive reaction. Reactions may be graded subjectively, or objectively using a scale of 1+ to 4+. A strong positive reaction may be approximately the size of the histamine response (3+).
c. If adverse reactions occur, see **OVERDOSAGE** for treatment recommendations.

ALLERGY IMMUNOTHERAPY: DOSAGE AND ROUTE OF ADMINISTRATION

The optimum dosage and route of administration of allergenic extracts has not been clearly established and many dosage schedules are currently in use.

Subcutaneous and sublingual-oral routes of administration are most commonly used for allergy immunotherapy. While intradermal injections allow for slower absorption of allergens, they are more difficult to administer and can be painful.

Allergen-specific immunotherapy is indicated in any patient where a diagnosis of atopy has been made, in which intradermal testing has enabled the identification of allergens that are likely to be contributing to the disease and in which allergen contact is unavoidable. In older patients or patients whose seasonal involvement is short, an alternate-day, short-acting oral corticosteroid or antihistamine may be the treatment of choice.

Subcutaneous hyposensitization is initiated using prescribed allergenic extracts in low doses as tolerated, and increased over time to reach, a maximum tolerated dose. Maintenance injections can be administered at 10- to 20- day intervals.[2-3] Sublingual-oral allergy immunotherapy is administered once daily, beginning with the lowest dose (50 microliters at 20,000 PNU/mL) for seven days, followed by seven days of 100 microliters (µL) at 20,000 PNU/mL, and then 140 µL at 20,000 PNU/mL as tolerated.

During the course of allergy immunotherapy, some patients may develop sensitivities to other allergens, even though signs to initially tested allergens being treated are controlled. Additional testing and treatment may be necessary.

TREATMENT

Selection of the allergenic extracts to include for use in immunotherapy is based on the degree of reaction to a specific allergen test (size of wheal) and clinical signs relative to patient history.

If the patient exhibits numerous sensitivities, the veterinarian may administer two treatment sets alternately. Most treatment mixtures consist of 12 or fewer allergens. If a new allergen is added to an existing treatment, the procedure for administration may be to begin with the primary schedule or build up from the refill schedule. This determination is at the discretion of the prescribing veterinarian.

If the patient also exhibits flea sensitivity, the veterinarian may treat with Flea Allergen separately. Food extracts are not recommended for use in allergy immunotherapy since their efficacy has not been established.

For allergy immunotherapy, the injection is administered subcutaneously using a 1.0 mL sterile tuberculin syringe, with a ⅝ to ½ inch, 25 to 27 gauge needle. Sublingual-oral allergy immunotherapy is administered under the tongue using non-sterile metered dose pumps to deliver 50 µL or 140 µL.

Initiate subcutaneous or intradermal allergy immunotherapy at 0.1 mL of a dilution that is 1/100 to 1/10 of the concentrated prescription dose then gradually increase the dose every 2-3 days until a determined maintenance dose or 1.0 mL of concentrate is reached. If intradermal injections are administered, the dose should not exceed 0.2 mL per injection site. If the patient is suspected to be extremely sensitive, lower doses or more dilute solutions may be used initially (200 PNU/mL), with gradually increasing doses similar to the suggested dosage schedule. Doses more dilute (less concentrated) than the concentrated strengths may be made by appropriate 1:10 dilutions with Normal Saline, Buffered Saline, or Glycerin Saline diluents containing phenol preservative such as, 0.5 mL of extract to 4.5 mL of diluent.

If the patient can tolerate higher doses, the schedule can be accelerated (such as, starting at a higher dose or concentration or by administering doses every 2 days rather than every 3 days) to reach a maintenance dose of 1.0 mL of the concentrate more quickly in fewer days.

A suggested treatment schedule is presented below. The dosage and length of treatment will depend on the reaction to and responsiveness of the patient.

SUGGESTED DOSAGE SCHEDULE FOR ALLERGENIC EXTRACT(S) SUBCUTANEOUS AND INTRADERMAL IMMUNOTHERAPY

Day	100 or 200 PNU/mL	1,000 or 2,000 PNU/mL	10,000 or 20,000 PNU/mL
1	0.1 mL		
4	0.2 mL		
7	0.4 mL		
10	0.8 mL		
13	1.0 mL		
16		0.1 mL	
19		0.2 mL	
22		0.4 mL	
25		0.8 mL	
28		1.0 mL	
31			0.1 mL
34			0.2 mL
37			0.4 mL
40			0.8 mL
43			1.0 mL*
53			1.0 mL
63			1.0 mL
Continue with 1.0 mL every 10 days.			

*Maintenance dose if tolerated; otherwise maintain at the highest tolerated dose (For smaller or more sensitive animals, the starting dosage concentrations may be 1/10 of those in the above table, beginning with 100 or 200 PNU/mL).

SUGGESTED DOSAGE SCHEDULE FOR FLEA ALLERGEN SUBCUTANEOUS AND INTRADERMAL IMMUNOTHERAPY

Week	1:100 w/v
1	0.1 mL
2	0.2 mL
3	0.3 mL
4	0.4 mL
5	0.5 mL
6	0.5 mL*
Continue with 0.5 mL every 10-21 days.	

*Maintenance dose if tolerated; otherwise maintain at the highest tolerated dose.

Once the maintenance dose is reached, the schedule is continued at approximately 20 day intervals until relief is evident, at which time the interval may be increased to greater than 20 days. The schedule may be modified to administer the doses pre-seasonally if the allergy is seasonal. If signs increase, intervals may be shortened. No maximum period of allergy immunotherapy has been determined and patients may have to undergo treatment indefinitely. If relief with allergy immunotherapy does not occur within nine months to one year, the treatment should be stopped and the patient reevaluated.

Sublingual-oral allergy immunotherapy is administered daily at a dose of 50 µL of a 20,000 PNU/mL extract for seven days. If tolerated, 100 µL of extract is given for seven days. Following this treatment, 140 µL is given as the daily maintenance dose. Sublingual-oral treatment usually does not exceed 140 µL.

SUGGESTED DOSAGE SCHEDULE FOR SUBLINGUAL - ORAL ALLERGY IMMUNOTHERAPY

Days	20,000 PNU/mL
1 - 7	50 µL
8 - 14	100 µL
15	140 µL
Continue with 140 µL daily.	

HOW SUPPLIED

GREER® allergenic extracts for veterinary use are available as sterile solutions with the protein content (PNU/mL) indicated on the label or weight/volume (w/v).

Treatment Extracts*	PNU/mL	w/v
Pollens	10,000 20,000 40,000	1:10 1:20 1:40 1:50
Fungi	10,000 20,000 40,000	1:10 1:20 1:40 1:50
Epidermals and Miscellaneous Inhalants	10,000 20,000	1:10 1:20 1:40 1:50 1:100
Insects	10,000 20,000 40,000	1:10 1:20 1:40 1:100
House Dust	10,000 20,000	1:1 1:2 1:5
Dust Mixtures		1:1 1:2 1:10
Mites		1:100
Intradermal Tests	1,000	1:1,000

*Other concentrations may be supplied when available.

Extracts are available in 5, 10, 30, and 50 mL vials for intradermal, subcutaneous and for preparation of sublingual-oral therapy vials. Extracts for diagnostic use only are supplied in 5 mL vials.

Extracts containing 50% glycerin are suitable for sublingual-oral use; however they should be diluted before use in intradermal testing. While 50% glycerin enhances stability, it may cause discomfort when injected.

STORAGE

Extracts should be stored at 2 - 8°C (36 - 46°F).

REFERENCES

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2. Griffin C.E., Hillier A. The ACVD task force on canine atopic dermatitis (XXIV): allergen-specific immunotherapy. *Vet Immunol Immunopathol*. September 20, 2001;81(3-4):363-383.
3. Rosser E.J., 1998. Aqueous hyposensitization in the treatment of canine atopic dermatitis: a retrospective study of 100 cases. In: Kwochka K.W., Willemse T., von Tscharner C., (Eds.), Advances in Veterinary Dermatology, Vol. 3. Butterworths/Heine, Boston, pp. 169-176

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L-512
Rev. 04/2014

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