

| 2016

Immunotherapy Manual



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Front photo: Oak, Balsam Lake Ontario, DWMoote

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Introduction to Immunotherapy Manual

Allergen immunotherapy is an effective treatment used by allergists for many common allergic conditions. It is perhaps the only patient treatment that is the primary purview of our specialty. Currently, it is the only identified disease-modifying intervention for allergic disease.

Many patients with allergic rhinitis or asthma do not respond sufficiently to appropriate allergen avoidance and medical therapy. Allergen immunotherapy may be an effective alternative for these patients. Immunotherapy has been proven effective in multiple randomized controlled trials, and systematic reviews. In spite of solid evidence, allergen immunotherapy is frequently underutilized or improperly utilized in Canada. There is also general agreement that immunotherapy has been an identified educational gap in Canadian Clinical Immunology and Allergy training programs.

With this updated immunotherapy manual, we hope to offer fellows in Clinical Immunology and Allergy a solid foundation in immunotherapy, which they can incorporate into their future clinical practice. We have attempted to provide practical information in a number of important areas of immunotherapy: its indications, allergen standardization, methods for mixing allergens, immunotherapy administration, and relevant safety issues.

We included several practice cases in allergen immunotherapy, where immunotherapy prescriptions are suggested, followed by explanations for the particular prescriptions. We recognize that not all allergists will write these prescriptions identically. The intention is to provide trainees with skills that they can build on, as they begin their independent practice. We expect that you will enjoy and better understand allergen immunotherapy after completing this manual.

We look forward to working with you in this key area of clinical allergy practice!

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Notice: Medical knowledge is constantly evolving. Clinical experience and continued developments in research bring about changes in treatment. The information published in this work is believed to be reliable and generally in accordance with the standards accepted at the time of publication. The examples provided in this manual are considered to be good practice but they are not intended to provide an exhaustive list of acceptable practices. Further, in view of the possibility of human error or changes in the medical science, neither the editors nor the publisher nor any other party who has been involved in the preparation or publication of this work guarantees that the information contained herein is in every respect accurate or complete. Readers are encouraged to verify the information contained herein with other sources. The Canadian Society of Allergy and Clinical Immunology and individual contributors to this manual will not be held responsible for any action taken or not taken based on or as a result of the reader's interpretation of the information contained herein.

Fundamentals of Allergen Immunotherapy

Effective in the management of:

- allergic rhinitis/conjunctivitis
- allergic asthma
- atopic dermatitis (2011 guidelines: “may be considered”)
- stinging insect (venom) hypersensitivity

Indications for immunotherapy

- symptoms induced by allergen exposure
- rhinitis as well as lower airway symptoms during peak allergen exposure
- antihistamines and topical corticosteroids do not sufficiently control symptoms
- pharmacotherapy causes undesirable side-effects.
- patients who do not want ongoing or long-term pharmacotherapy

Allergens for which there is evidence based efficacy in allergic rhinitis/conjunctivitis

- birch
- grass
- ragweed
- parietaria
- house dust mite
- cat
- Alternaria
- cockroach

Allergens for which there is evidence based efficacy in asthma

- grass
- ragweed
- house dust mite
- cat
- dog
- Alternaria

Venom immunotherapy

- individuals of all ages with anaphylactic reactions to stinging insects as well as adults with generalized reactions limited to the skin

Special considerations

- young children less than 6 years of age
- pregnancy
- the elderly
- patients with malignancy, immunodeficiency and autoimmune diseases

Contraindications

- patients on beta-blockers (relative contraindication with venoms)
- patients with uncontrolled or severe asthma
- significant co-morbid diseases such as cardiovascular disability

Important Allergens

Insect venoms

- Hymenoptera

- imported fire ant

Respiratory allergenic proteins

- Bet v 1 (birch pollen)
- Phl p 1 and Phl p 5 (grass pollen)
- Amb a 1 (ragweed pollen)
- Fel d 1 (cat)
- Der p 1, Der p 2, Der f 1 and Der f 2 (house dust mites)
- Can f 1 (dog)
- moulds; especially Alternaria, Cladosporium (older name: Hormodendrum)
- cockroach

Biovariability of allergens

- variable expression and the variance of individual allergen entities and levels in source materials
- different production processes
- individual patient differences in immune reactivity

Standardization of Allergens

Standardization

- ensure a consistent composition and potency of production batches
- overall IgE binding capacity of an allergen extract is related to content of one major allergen or several allergens

Standardization process in the US

- allergen extracts are compared with reference allergens with specific potency standards using skin testing. Cat and ragweed standardization is based on major allergen content.
- demonstrate batch-to-batch consistency
- compliance with the standard

19 standardized allergenic extracts are available

- hymenoptera venoms (six)
- house dust mites (two)
- cat extracts (two)
- short ragweed pollen (one)
- grass pollens (eight)

Standardization of allergens and Unit Definitions

The US and European (Nordic) systems of biological standardization are different. Both are based on the quantitative evaluation of skin tests. The US method (ID50EAL) uses intradermal testing in 15 highly sensitized individuals and a threefold dilution series of the allergen extract. The longest measurement of the skin test erythema and the midpoint orthogonal diameters are measured and added resulting in the 'sum of erythema' (in mm).

The values for the different dilution steps are graphed and the dilution is calculated that would induce a sum of erythema of 50 mm (D_{50}). A D_{50} of 14 is arbitrarily assigned 100,000 bioequivalent allergen units (BAU) per ml. The allergenic potency of a new batch is calculated by the formula $BAU/ml = 100,000 \times 3^{(D_{50}-14)}$.

The European (Nordic) method utilizes the skin prick test in highly and moderately sensitized individuals ($n = 20$), the wheal size is measured using histamine at a concentration of 10 mg/ml as the reference and an allergen extract that results in the same wheal size is assigned 10,000 biological units (BU).

Biochemical and immunochemical methods can be used to control the consistent composition and activity of allergen products. The most common method for measurement of total allergenic activity is the competitive IgE-binding inhibition test [e.g. previously radioallergosorbent test (RAST) inhibition, now enzyme allergosorbent test inhibition]. However, the test(s) neither reflects the ability to cause allergic symptoms nor the therapeutic potential of the product (i.e. immunogenicity/immunomodulation).

Measurement of the concentration of individual major allergens, thought to correlate with the biological potency of allergen extracts¹ would further the standardization of allergen products.²

¹ Dreborg S, Einarsson R. The major allergen content of allergenic preparations reflects their biological activity. *Allergy* 1992; 47:418-423.

Nine manufacturers produce more than 200 fungal allergen extracts, and none has been standardized in the United States. The only candidate reference available is an *Alternaria alternata* extract prepared by an international collaborative study.³ Fungal allergen products manufactured by different companies with identical labelling are not quantitatively or qualitatively similar.

Each allergen extract manufacturer uses its own assays and rarely compares specific antigen concentrations with those of other manufacturers. There remain significant differences between corresponding extracts, both standardized and not, from the different manufacturers.⁴

The level of quality control for the 19 standardized allergen extracts is the exception rather than the rule. In vitro potency tests that correlate with in vivo clinical responses have not been developed for the hundreds of non-standardized extracts available.

Even for standardized extracts the acceptable range for potency have release limits for standardized dust mite and grass pollen allergen extracts of 0.5 to 2.0⁵

² Grier TJ, Hazelhurst TM, Duncan EA, et al. Major allergen measurements: sources of variability, validation, quality assurance, and utility for laboratories, manufacturers, and clinics. *Allergy Asthma Proc* 2002; 23:125-131.

³ Helm RM, Squillace DL, Yunginger JW: Production of a proposed international reference standard *Alternaria* extract. II. Results of a collaborative trial, *J Allergy Clin Immunol* 81:651, 1988

⁴ Dirksen A, Malling H.-J, Mosbech H. et al. HEP versus PNU Standardization of Allergen Extracts in Skin Prick Testing. A Comparative Randomized in Vivo Study. *Allergy* Vol 40 Iss8, Pages 620 – 624 Published Online: 28 Apr 2007

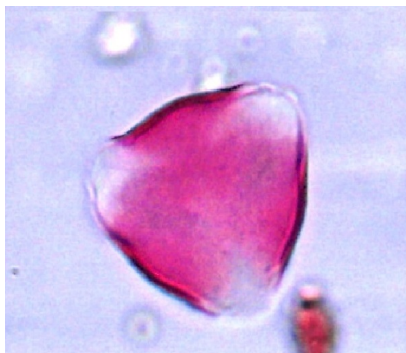
⁵ Slater JE: Draft guidance for reviewers: potency limits for standardized dust mite and grass allergen vaccines: a revised protocol, 2000.

Aerobiology varies with geographic location

Aerobiology

- transport of windborne biological particles
- dependent on local flora and weather conditions
- particles usually < 60 μm in diameter
- it is important to know the timing and concentration of suspect pollens in local geographic areas
- pollen photos are also available on the American Academy of Allergy, Asthma & Immunology website: <http://www.aaaai.org/about-aaaai/newsroom/photo-gallery/photos---graphics--pollen>

Pollen Photos (courtesy Jim Anderson MLT, Aerobiologist)



Acer negundo (box elder): 3 furrows bulging out of the thin furrow surface – turgid appearance, coarse surface, 25-35 μ



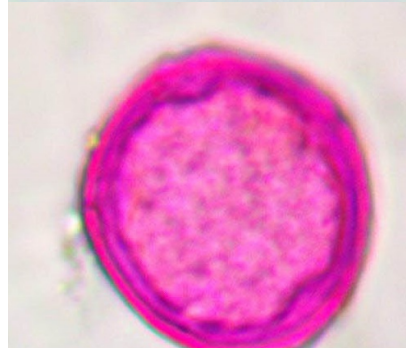
Ash: usually 4 short furrows with jagged edges, surface finely reticulate, 22-28 μ



Birch: smooth surface, usually 3 prominent pores above a thick “collar”, 20-32 μ



Cedar/juniper: no pores or furrows, distinct circular to star-shaped heavy interior surrounded by a very thin surface



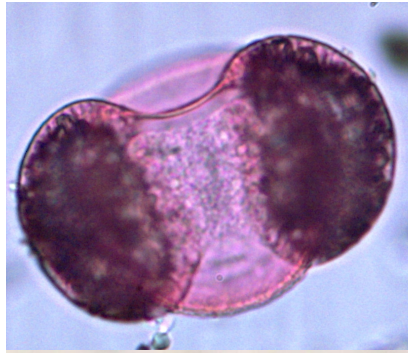
Elm: usually 5 not easily seen pores, pentagonal shape, surface somewhat like ground glass, 25-35 μ



Alder: 20-26 microns; usually 4-5 distinct pores



Hickory: large (40-50 μ), smooth to granular surface, a triangle of 3 pores



Pine: large (50-85 μ), most distinct feature is 2 large coarse surfaced air-filled bladders rendering a "Mickey Mouse cap" appearance



Maple (sugar maple): 3 long furrows, reticulated surface, 25-35 μ



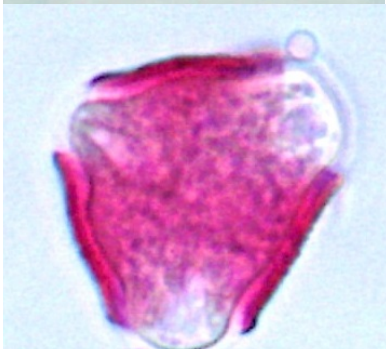
Poplar: no pores or furrows, surface finely granular, appearing to be cracking/flaking, 25-35 μ



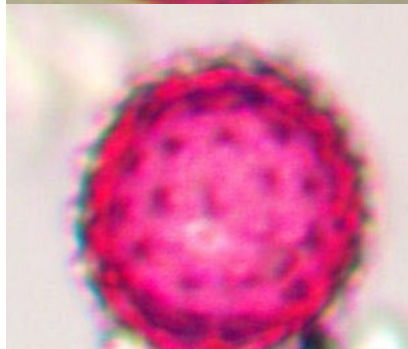
Mulberry: small (19-23 μ), usually 2 spores with distinct nipple, stains lightly



Walnut: large (36-41 μ), 10-15 distinct pores around one or two hemispheres



Oak: 3 bulging furrows, surface often described as "peanut shell" in texture, 24 X 30 μ



Ragweed: distinct spiny appearance, spins are rounded-never pointed, three indistinct short furrows with a pore, on the small side (about 20 μ)



Grass: smooth surface with one prominent pore, usually 30-40 μ

Samples were obtained with a Burkard pollen/spore trap at the London ON AAAAI/NAB station. The pollen grains were expanded & stained with a phenosafarin in glycerin jelly preparation in order to make distinguishing morphological features more evident. These include surface markings, pores, and furrows.

British Columbia: Coastal British Columbia

Tree pollen

- early February until mid-July, with the highest counts lasting until mid-June.
- primary deciduous trees
 - alder, birch, poplar
 - other deciduous trees such as elm and oak may also contribute

grass pollen

- end of April/beginning of May until September
- highest grass concentrations: early June to mid-July

Weed pollens not usually a major factor

- no native ragweed

mould spores

- mould spores are present throughout the year except for a few weeks of the year when the ground remains frozen all day
- further increase in September and October
- the two most prevalent mould spores are:
 - *Cladosporium*
 - basidiomycetes

British Columbia: Interior

Tree pollen

- starts in late March until mid-July
- primary deciduous trees
 - birch, poplar, willow

Grass pollen

- may start on the 1st of May in the southern part of the province
- occurs up to a month later in the Northern parts.

Sagebrush

- can occur in the southern part of the province in September

Ragweed

- is minimal

Mould

- *Cladosporium* can occur in April until the late fall months

Prairie Provinces

Tree pollen

- starts in the first week of April until June
- main deciduous trees
 - birch, poplar
 - alder, maple, elm, oak, ash, and willow may also contribute

Grass pollen

- starts in mid-May until the end of September

- peak season is usually mid-June until early July.

Most common weeds

- nettles, sage brush
- some ragweed—especially in Manitoba

Mould spores

- can occur through the spring, summer, and early fall (Alternaria, Cladosporium)

Ontario and Quebec

Tree pollen

- early April in southern Ontario and Quebec
- may occur 4-6 weeks later in Northern parts

Tree pollen: Southern Ontario

- most common deciduous trees:
 - mulberry, maple & Box Elder, poplar & willow, oak, beech, birch & alder, and ash
 - walnut & hickory, birch, elm, sycamore, and conifers (including pine and juniper) may also cause contribute

Tree pollen: Northern Ontario

- birch, poplar

Tree pollen: Quebec

- ash, poplar, birch
- maple, alder, oak are less prevalent

Grass pollen

- mid-late May and a couple of weeks later in the northern part of province
- latter part of May and mid-June are in the peak seasons for grass pollination

Ragweed pollen

- Southern Ontario and Southwestern Quebec
- Early-mid August in the southern part
- reaches a peak in late August or early September
- stops at first frost (variable)
- nettle and plantain can also contribute

Mould spores

- throughout the spring, summer, and fall
- concentrations may be higher late summer to fall in Quebec
- Alternaria and Cladosporium are the predominant outdoor moulds

Maritimes & Newfoundland/Labrador

Tree pollen

- late March until last week of June
- deciduous trees:
 - birch, poplar
 - alder, maple, oak and ash can contribute

Grass pollen

- mid-May until the end of September
- peak is early June

Ragweed

- early August until the end of September

Mould spores

- particularly during the later summer and early fall
- Alternaria, Cladosporium

Mixing of Allergens

- some allergens contain proteolytic enzymes
- proteolytic enzyme containing extracts may degrade other extracts
- where possible, do not mix these with other allergens
- results in immunotherapy prescriptions with allergens separated into distinct sets
- some allergens are resistant to proteolytic enzymes

Allergens with protease activity (may be mixed with each other but not low protease allergens)

mould
cockroach

Allergens with low protease activity (may be mixed with each other)

trees
grass
ragweed and other weeds
animals (cat and dog)
dust mites

NB: ragweed, animal and dust mite antigens are resistant to protease activity and could be included with members of either category^{6,7,8}

Therapeutic Allergen Dosage

Target Doses of Immunotherapy

- 6 mcg dose is appropriate minimal maintenance dose
- far lower doses no more successful than placebo
- single antigen trials succeed with doses higher than 6 mcg
- wide variety of acceptable doses
- the more antigens that are included, the more difficult it is to attain adequate dosing. Typically, this is around maximum four antigens per vial, but this depends on the concentration of each antigen. This is especially problematic for dog antigen, which varies in US and Canada (see further discussion in problem #4). For a full discussion of the mechanics of mixing the antigens, please see the American Academy of Allergy, Asthma & Immunology Practice Parameters. This is especially important if you plan to write the ABAI exam.

⁶ Esch, RE. J Allergy Clin Immunol 2008;122:659-60.

⁷ T.J. Grier et al. / Ann Allergy Asthma Immunol 108 (2012) 439–447

⁸ Thomas J. Grier et al. / Ann Allergy Asthma Immunol.2007;99:151–160

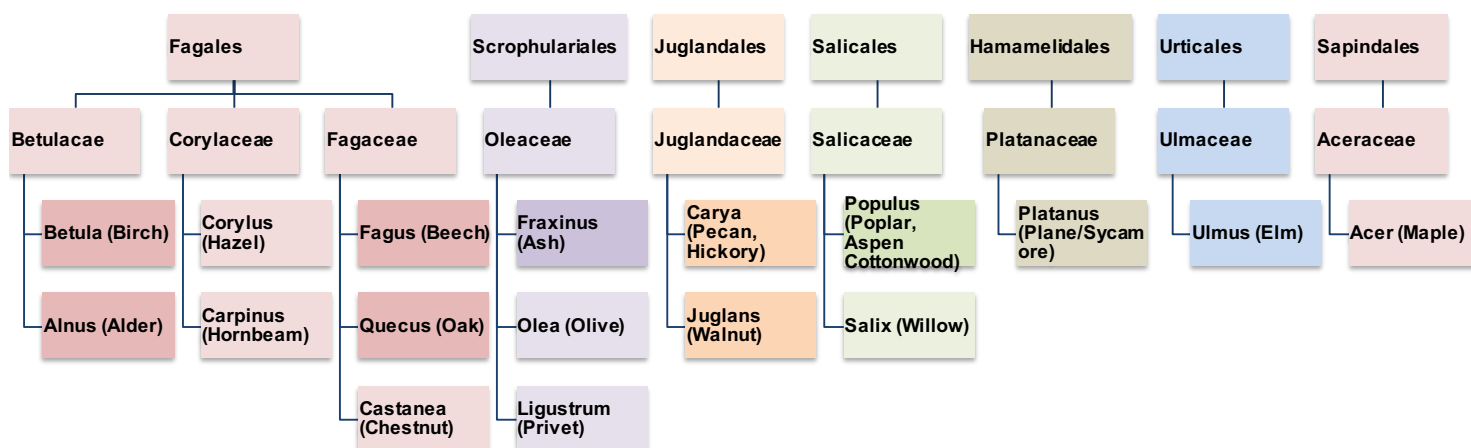
Tree Pollen

Tree pollen presents a unique problem because they do not cross react much with each other. In general, we should make sure that the mix chosen represents the trees that are relevant to your geographic area, and match the patient's sensitization. This highlights why it is important to test with individual trees and not just a tree mix. In addition, it is reasonable to choose pollens that are representative of a cross-reactive group (e.g. oak and birch belong to the same family and may be considered cross-reactive).

Relevant cross-reactivity includes:

- poplar & willow
- oak, beech, chestnut, birch, alder
- ash
- pine & juniper
- walnut & hickory
- elm
- sycamore
- mulberry

Tree Pollen Taxonomy



		2003 Practice Parameter			Nelson 2007	2007 Practice Parameter	2011 Practice Parameter	CSACI recommended dose/ml
Allergen	Major Allergen	Dose, standardized units	Dose, major allergen		Effective dose range (per dose)	Effective dose range (per dose)	Effective dose range (per dose)	Dose per ml, presuming 0.5 ml/dose
D. pteronyssinus	Der p 1	600 AU	7-12 mcg		7-12 mcg	500-2000 AU/dose	500-2000 AU/dose	2000 AU
D. farinae	Der f 1	2000 AU	10 mcg		10 mcg		500-2000 AU/dose	2000 AU
Dust mite mix								1000 AU ea
Cat (pelt or hair)	Fel d 1	2000-3000 BAU	11-17 mcg		11-17 mcg	1000-4000 BAU	1000-4000 BAU	2000 BAU
grass (Timothy)	Phl p 5	4000 BAU	7 mcg		15-20 mcg	1000-4000 BAU	1000-4000 BAU	5000 BAU
Short ragweed	Amb a 1		6-24 mcg		6-24 mcg	6-12 mcg 1000-4000 AU	6-12 mcg 1000-4000 AU	5000 PNU
Other pollen (non-standardized) e.g. Tree Mix		NA	ND	1:100-1:30		Highest tolerated dose	0.5 ml of 1:100 or 1:200 wt/vol	5000 PNU
Fungi/mould (non-standardized) e.g. Cladosporium or Alternaria		NA	ND	1:100-1:50		Highest tolerated dose	Highest tolerated dose	5000 PNU
Birch	Bet v 1			1:100-1:50	3.28-12 mcg	Highest tolerated dose		5000 PNU
Dog	Can f 1				15 mcg	15 mcg	15 mcg of Can f 1	5000 PNU*
Hymenoptera							50-200 mcg of each venom	100 mcg/ml, NB: 1 ml dose
Fire Ant							0.5 ml of 1:100 wt/vol up to 0.5 ml of 1:10 wt/vol	

Note: Some prescriptions are written per dose, and others per ml. Exercise caution! CSACI guideline dosing for aeroallergens is not in mcg because accurate dosing with mcg is not consistently available in Canada.

*Insufficient data: Current Canadian products for dog allergen cannot achieve the 15 mcg dose achievable with acetone precipitated dog allergens available in the US. The PNU recommendation approximates previous recommendations for wt/vol. See case # 4, pg. 33.

Practical Safety Issues

Anaphylaxis in the Office Setting

Allergy skin testing and allergen immunotherapy may cause severe and even fatal anaphylaxis. Physicians who perform allergy skin tests and administer allergen immunotherapy must know how to manage anaphylaxis

Allergy skin tests

- Systemic reactions: 0.3% of intradermal venom allergy skin tests⁹
- Systemic reactions in allergy skin prick testing: 77 per 100,000 or 0.07%¹⁰

Allergen immunotherapy

- Systemic reactions: 1-4% of patients on inhalant subcutaneous immunotherapy¹¹
- In a recent study, there were no fatalities in about 8.1 million injections¹²
- With subcutaneous immunotherapy, there is a risk of intradermal and intramuscular injections. The depth of the injections should be considered to assure injection into the subcutaneous space
- The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System is useful to help standardize the severity of reactions¹³

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present Cutaneous Generalized pruritus, urticaria, flushing, or sensation of heat or warmth or Angioedema (not laryngeal, tongue or uvular) or Upper respiratory Rhinitis—(e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to originate in the upper airway, not the lung, larynx, or trachea or Conjunctival Erythema, pruritus or tearing Other Nausea, metallic taste, or headache	Symptom(s)/sign(s) of more than 1 organ system present or Lower respiratory Asthma: cough, wheezing, shortness of breath (e.g. less than 40% PEF or FEV ₁ drop, responding to an inhaled bronchodilator) or Gastrointestinal Abdominal cramps, vomiting, or diarrhea or Other Uterine cramps	Lower respiratory Asthma (e.g. 40% PEF or FEV ₁ drop NOT responding to an inhaled bronchodilator) or Upper respiratory Laryngeal, uvula, or tongue edema with or without stridor	Lower or upper respiratory Respiratory failure with or without loss of consciousness or Cardiovascular Hypotension with or without loss of consciousness	Death

Adapted from Cox et al. *J Allergy Clin Immunol* 2010

1. Be prepared for an anaphylactic reaction

- Physicians who perform allergy skin tests and allergen immunotherapy must be familiar with risk factors predisposing to anaphylaxis

⁹ Quirt et al *Ann Allergy Asthma Immunol* 116 (2016) 49-51

¹⁰ Lin et al *Ann Allergy Asthma Immunol* 115 (2015) 229e233

¹¹ Phillips et al. *Allergy and Asthma Proceedings*, Volume 32, Number 4, July/August 2011, pp. 288-294(7)

¹² Epstein TG, Murphy K, Bernstein DI. Fatal and Systemic Reactions to Subcutaneous Immunotherapy: ACAAI/AAAAI National Surveillance Study After One Year. *Ann Allergy Asthma Immunol* 2009;103:A23.

¹³ Cox et al. *J Allergy Clin Immunol*. 2010 Mar;125(3):569-74, 574.e1-574

- Review with staff their roles during an anaphylactic reaction
- Have emergency medications, oxygen, and equipment required for the treatment of anaphylaxis organized in one area of your office or clinic area (on a crash-cart or in a readily accessible area)
- The receptionist should be ready to call 911 when instructed

2. Signs and Symptoms

Urticaria, angioedema	87%
Dyspnea	59%
Dizziness, syncope	33%
Diarrhea, abdominal cramps	29%
Flushing	25%
Upper airway edema	21%
Nausea, vomiting	20%
Hypotension	15%
Rhinitis	8%
Itch without rash	5%
Seizure	1%

adapted from—Webb et al: Ann Allergy Asthma Immunol 2006; 97: 39-43

- Anaphylaxis typically involves the cutaneous, GI, respiratory, and cardiovascular systems
- Signs and symptoms are unpredictable and may vary from patient to patient. Not all organ systems may be involved simultaneously
- The absence of cutaneous symptoms does not rule out anaphylaxis, and should not delay the administration of epinephrine

3. Time course

- The onset of anaphylaxis may be within minutes or up to an hour or two
- In studies of anaphylactic fatalities secondary to skin tests and allergen immunotherapy, most documented fatalities (73%) occurred within 30 minutes of the injection

4. Medications required in the office setting

- **Epinephrine 1:1000 (most important)**
- Oral and injectable antihistamines
- Intravenous (IV) corticosteroid
- Salbutamol or comparable fast-acting bronchodilator
- Glucagon (especially for treatment of anaphylaxis in patient on beta-blocker)
- Tourniquets
- IV access and IV tubing for fluids
- Normal saline or Ringer's lactate in 500 ml bags
- Oxygen
- Ambu-bag
- Oropharyngeal airway

5. Management of acute anaphylaxis

- Administer epinephrine 0.3 to 0.5 ml intramuscularly (IM) in the thigh for adults or 0.01 mg/kg (up to 0.3 ml) epinephrine IM in the thigh for children. Epinephrine may be administered every 5 to 10 minutes, as indicated
- Apply tourniquets proximal to the injection site(s). (*monitor patient for ischemia of the distal limb(s)*)
- A rapid assessment of the patient's state of consciousness, airway, blood pressure and pulse
- Place patient on the back if the patient has symptoms or signs of hypotension, or in a position of comfort if there is respiratory distress. Elevate the lower extremities.
- If respiratory symptoms are present, administer oxygen by mask
- If there is bronchospasm, unresponsive to epinephrine, treat with a fast-acting bronchodilator (e.g. salbutamol by metered dose inhaler 8 to 10 puffs or Ventolin mask nebulization)
- If there are symptoms/physical finding of oropharyngeal obstruction, or lack of responsiveness to epinephrine, intubation may be necessary
- If the systolic blood pressure remains less than 80-100mm Hg, and/or pulse is weak, and the situation is refractory to the initial dose of IM epinephrine, administer large volumes of fluids (e.g. normal saline or Ringer's lactate) rapidly-see below
- Intravenous epinephrine may be considered in cases where cardiovascular collapse or impending cardiovascular collapse that is refractory to IM epinephrine and volume resuscitation, and an epinephrine infusion is not yet available. This is best administered by slow push of 0.5 to 1 mL of 0.1 mg/mL (1:10,000) epinephrine solution¹⁴
- If the patient is on a beta-blocker, consider administering epinephrine at doses as detailed above and note its effect. If the patient does not respond favourably to epinephrine, consider administering glucagon IV
- An ambulance (or 911) should be called by the receptionist or the clinic nurse, at the discretion of the attending physician, and concurrent with treatment as appropriate.
- The patient should be sent to emergency for further observation

6. Adjunctive therapies

- (antihistamines, corticosteroids, bronchodilators) should not be given until after the administration of epinephrine
- Oxygen
- IV fluids with Ringers Lactate/Normal Saline
- Adults: Normal saline or Ringer's lactate: 1000 to 2000 ml in first hour
- Children: Normal saline or Ringer's lactate: 30 ml/kg in first hour
- Diphenhydramine: 1mg/kg IV/IM (max dose 50-100 mg)
- Solu-Medrol: 2 mg/kg IV/IM (maximum dose 125 mg)
- Ranitidine: 1 mg/kg IV (maximum dose 50 mg)
- Glucagon: 0.1 mg/kg IV/IM for refractory hypotension for patients on beta blockers (1 mg slow IV push over 2 minutes)

7. After the episode, review the dose of extract administered and relevant history to determine if there is an identifiable cause for this allergic reaction.

- Determine whether you feel it is safe to continue allergen immunotherapy. If too dangerous, arrange a follow-up visit with the patient and discuss your recommendations

¹⁴ J Emerg Med. 2014 Aug;47(2):182-7. doi: 10.1016/j.jemermed.2014.04.018. Epub 2014 Jun 2.

- If you determine that it is safe for the patient to continue allergen immunotherapy, arrange a follow-up visit and determine if the patient is willing to continue. If patient is an asthmatic, optimize patient's asthma control
- If allergen immunotherapy is to continue, adjust the next dose of allergy extract to 10% of previous dose (for severe anaphylactic reactions) or 50% of previous dose (for mild systemic allergic reactions).
- Be careful as the previous dose of allergen immunotherapy that caused the reaction is approached. Half-step increments may be helpful.

8. Prevention of anaphylaxis

- Recognize risk factors which place patients on allergen immunotherapy at risk for anaphylaxis (see below)
- Use more dilute concentration for initial dose and slower build up in more sensitive patients (based on history or skin tests)
- Have a properly equipped office (see above)
- Optimize office procedures to reduce nursing and clerical errors
- Mandatory observation of patients for 30 minutes post allergen immunotherapy
- Education of patients and office staff to recognize early symptoms of anaphylaxis
- Avoid exercise for at least 2 hours post injection
- Consider avoiding allergen immunotherapy injection if fever, respiratory infection, or increased allergy symptoms

9. Increased risk factors for anaphylaxis

- Uncontrolled asthma and/or FEV $< 70\%$ predicted
- Asthmatic symptoms present immediately before receiving allergen immunotherapy
- Concomitant treatment with beta-blockers, ACE inhibitors
- Previous history of systemic reactions to allergen immunotherapy
- Allergen immunotherapy from new maintenance vials
- Intravascular injection
- Dosing errors

10. When to reduce the dose

- Longer than scheduled interval (see end of document)
- New extract vial (decreases ranges from a third to a half reduction of first dose from new vial)
- Reaction to prior dose
- Peak pollen season—may choose to keep dose the same or reduce, depending on patient sensitivity

Sublingual Immunotherapy

Sublingual tablet immunotherapy is a novel way to desensitize patients, where tablets are placed under the tongue, and is currently available for the treatment of grass and ragweed allergy. Up until now, immunotherapy has only been administered by subcutaneous injection. Similar to injections, patients who receive sublingual immunotherapy demonstrate modulation of their immune system's response to the allergen being administered, resulting in increased tolerance to that allergen. The grass and ragweed tablets currently available have been studied in numerous rigorous clinical trials. These studies have shown that the symptoms and the medication requirements improved with active treatment compared to placebo. Some advantages to this type of immunotherapy compared to injection immunotherapy include improved safety, with fewer systemic allergic reactions, and the ability to administer the immunotherapy tablets at home.

The first product introduced in Canada was a grass immunotherapy tablet called Oralair®. This tablet is given at a dose of 100 IR (Index of Reactivity) in the allergist's office about 16 weeks before the onset of grass pollen season. The second dose is, 200 IR and is taken at home the next day, followed by 300 IR per day. This is taken until the grass season is over. The other available grass sublingual immunotherapy tablet is Grastek®. The first dose is taken in the allergist's office 8-12 weeks before the grass pollen season at a dose of 2,800 BAU (Bioequivalent Allergy Units), and then the same dose is taken daily at home until the end of grass pollen season.

The ragweed product is called Ragwitek®, and each tablet is dosed at 12 amb a 1-U (Units). The first dose is taken at the allergist's office, and then the same dose is taken at home. This is started 12 weeks before ragweed season, and is taken daily until the end of ragweed season. Health Canada has approved the following ages groups for which the different products can be prescribed. These are Grastek®: (5-65 years of age), Oralair®: (5-50 years of age) and Ragwitek®: (18-65 years of age) .

With regards to side effects, approximately 40% of patients will have local symptoms such as oral itchiness, throat discomfort, and ear discomfort. Generally, these reactions are short-lived and are present mainly in the first week of therapy. These symptoms typically occur during the first week or so of treatment. Pretreatment with non-sedating antihistamines may be helpful for local symptoms. There is a very small risk of more severe systemic allergic reactions with this type of immunotherapy. Because of this small risk, some allergists may offer the patient an epinephrine auto-injector to keep available in case a reaction occurs at home. The risk of systemic allergic reactions is much lower with sublingual immunotherapy compared to traditional allergy injections.

Sublingual immunotherapy has been available in Canada since 2013. There are still a number of questions regarding sublingual immunotherapy. For example, there is little data with respect to using both grass and ragweed sublingual immunotherapy safely together in a single patient. (one publication⁹) The long-term protective effects of these sublingual immunotherapies must be studied. Importantly, there could be some risk of other side effects such as aggravating or causing eosinophilic esophagitis.

In summary, sublingual immunotherapy is a new, home based therapy approved for treatment of allergic rhinitis caused by grass and ragweed pollen allergy in adults (grass and ragweed) and pediatrics (grass).

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Immunotherapy Practice: Cases



Problem 1

Patient History and Physical Examination

- 17 year old female with a 10 year history of nasal congestion
- symptoms have been perennial, but keep her awake in August and September
- antihistamines and 4 months of daily intranasal steroids have not relieved her symptoms
- her mother had been on immunotherapy previously and she would like her daughter to try immunotherapy
- on nasal examination, inferior turbinates were pale and congested, chest was clear

Allergy Skin Tests

D. farinae	6 mm wheal
D. pteronyssinus	5 mm wheal

Worksheet

House Dust Mite Prescription

Treatment set 1

Maintenance concentration final vial

- D. farinae 1000 AU/ml
- D. pteronyssinus 1000 AU/ml

Number of dilutions: 4, Volume: 10 ml

Final Maintenance Dose 0.5 ml/injection:

- D. farinae 500 AU
 - D. pteronyssinus 500 AU
-

Explanation

Rationale for Immunotherapy	• Patient has persistent symptoms of allergic rhinitis which worsen in August and September • Recommended medical therapy was not effective
Choice of Allergen(s)	• D farinae (Der f 1) and D pteronyssinus (Der p 1) • Her symptoms are consistent with allergy to house dust mites, to which she is positive on allergy skin tests.
Dosing	CSACI recommended prescription: • Der p 1 or Der f 1: 2000 AU/ml per allergen • because of significant cross-reactivity between Der p 1 and Der f 1, a mix of 1000 AU/ml each has been prescribed • maintenance dose per 0.5 ml maintenance injection: ○ 500 AU for each of Der p 1 and Der f 1 or 1000 AU total per dose Practice parameter: Effective dose range for Der p 1 is 7-12 mcg and for Der f 1 is 10 mcg. This is in the range of 500-2000 AU per 0.5 ml maintenance dose • The combined 1000 AU/dose is at the lower end of the effective dosing range.

Formulation and Compounding Explanation for House Dust Mite Case

The formulation and compounding of allergy immunotherapy extract follows after establishing that the patient is a good candidate for desensitization. The assessment of the allergy patient by a comprehensive and directed history and physical examination, and the demonstration of sensitization to the relevant allergen(s) determine which allergens should be included in the immunotherapy extract.

The target dose is based on the dose range found to be effective in clinical trials. The extract is formulated and compounded as in the following example. Dose may be set at a lower level for very highly sensitized individuals or additional dilutions are made for the induction phase of treatment. In this manual we recommend using a set with four dilutions. Generally, this number of dilutions is tolerated with even highly sensitized patients.

Example

For a house dust mite extract it is decided that the target dose is 500 AU of house dust mite *Dermatophagoides farinae* (Der f) and 500 AU house dust mite *Dermatophagoides Pteronyssinus* (Der p) and that this dose is to be delivered in a 0.5 mL volume of solution.

Formulation

The bulk antigen solution used for formulation should be similar to the solution that was used for skin prick testing or serological IgE quantification. Specifically, for this example, an allergist might have tested with house dust mite mix made of 50% Der f and 50% Der p or separately with each of the house dust mites. The extract should be compounded from bulk solutions of Der f and of Der p mix or separate mite solutions respectively. This will yield an extract that parallels test results. They are not interchangeable.

The administration volume is arbitrary and variable but is determined by such a volume so that the viscosity of the solution will be low enough to flow into and out of the administering needle, that the volume of glycerine will be kept to a minimum as it can be irritating, that the chosen volume will be easily accommodated subcutaneously without tissue expansion and that will accommodate adequate amounts of fluid so the appropriate number of antigens can be incorporated.

The total volume of the vial is arbitrary, but is chosen so that enough solution will be available to withdraw the required number of injections as designated by the immunization schedule and allow for 10-15% wastage. There is evidence that large volumes will affect extract potency particularly in dilute extracts stored at low volumes. This is presumed to be due to protein adhering to the vial wall.¹⁵ More dilute extracts that are in relatively small volumes are more susceptible to loss of potency. A calculation should be made so that there is enough solution to fulfil the schedule up to the expiry date. The calculations are confirmed and checked before immunotherapy sets are compounded.

Compounding in the immunotherapy laboratory

This prescription example would require there to be 1000 AU of Der f 1 and 1000 AU of Der p 1 in each ml of solution. Calculations are done for each antigen in the formulation and are done each time. If for this example a 10 ml vial is used, and we need 1000 AU of Der f 1 and 1000 AU of Der

¹⁵ Nelson HS Effect of preservatives and conditions of storage on the potency of allergy extracts. Journal of Allergy & Clinical Immunology. 1981 Jan; 67(1):64-9

p 1 in each ml of solution so there must be a total of 10,000 AU of Der f 1 and a total of 10,000 AU of Der p 1 for the total volume of 10 ml.

Der f 1 and Der p 1 stock solutions are usually available as 10,000 AU per ml; therefore 1 ml of each will be introduced into the 10 ml vial. This will be a total of 2 mL volume. The remaining volume will be made up of saline with phenol and possibly with or without human serum albumin. A 50% glycerol saline solution can be used. Phenol is an antibacterial and albumin stabilizes the protein and coats the vial surface to reduce allergen protein absorption.

This vial now contains the final desired concentration for the desired dose in the desired injection volume. This is “full strength” extract.

During the induction phase of immunotherapy dilutions are made from this full strength extract vial so that the patient can be slowly brought up to therapeutic dose with a reduced chance for a systemic anaphylactic reaction.

To create a more dilute solution [e.g. 1:10] an aliquot of the full strength solution is mixed with a nine-fold volume of the diluent. Sequential even more dilute solutions [1:100 and 1:1000] are made by repeatedly using 1 volume of with 9 volumes of diluent from the previous more concentrated vial.

Problem 2

Patient history and physical examination

- 14 year old female with a 2 year history of nasal congestion and itchy eyes from August until October
- antihistamines have not helped her nasal congestion
- she dislikes intranasal steroids and does not want to put anything “up her nose.”
- she has trouble sleeping and also has symptoms of day and night time cough
- nasal examination was normal and chest was clear
- spirometry was normal with no evidence of reversibility

Allergy Skin Tests

Alternaria	6 mm wheal
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Worksheet

Alternaria Prescription

Treatment set 1

Maintenance concentration final vial:

- Alternaria 5000 PNU ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- Alternaria 2500 PNU
-

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinitis • Recommended medical therapy was not effective • Patient dislikes intranasal steroids • Therefore reasonable to prescribe immunotherapy
Choice of Allergen(s)	• Alternaria • Patient has allergic rhinitis that is timed with the Alternaria season, and a positive allergy skin test to Alternaria
Dosing	CSACI recommended prescription: • Alternaria: 5000 PNU/ml • maintenance dose per 0.5ml maintenance injection: ○ Alternaria 2500 PNU Practice parameter: Effective dose range for Alternaria is the “highest tolerated dose” per 0.5 ml maintenance dose which is an impractical start point, hence CSACI recommendation is used

Problem 3

Patient History and Physical Examination

- a firefighter is required to make home visits several days a week for fire prevention
- in households with cats, she develops symptoms of wheezing and rhinoconjunctivitis
- she is not cat exposed at home
- although these symptoms are partially managed by bronchodilators and antihistamines, they interfere with her normal daily activities
- she doesn't have asthma symptoms at other times, and feels that she does not require daily asthma prophylaxis
- she would like to have preventive immunotherapy

Allergy Skin Tests

Cat pelt	7 mm wheal
Cat epithelium	7 mm wheal
Dog hair/dander	2 mm wheal

Worksheet

Cat Prescription

Treatment set 1

Maintenance concentration final vial:

- Cat antigen 2000 BAU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- Cat antigen 1000 BAU
-

Explanation

Rationale for Immunotherapy	• Patient has asthma and rhinoconjunctivitis on cat exposure, which is unavoidable in her work environment: • Not exposed to cat in her home • Recommended medical therapy was not effective • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• Cat
Dosing	CSACI recommended prescription: • cat: 2000 BAU/ml • maintenance dose per 0.5 ml maintenance injection: ○ Cat: 1000 BAU Practice parameter: Effective dose range for cat is 1000–4000 BAU per 0.5 ml maintenance dose • Aim for the low end of the therapeutic range, and adjust upward after 1 year if it is not effective

Problem 4

Patient History and Physical Examination

- 26 year old veterinary student has noticed consistent symptoms of nasal congestion, rhinorrhea and sneezing as well as ocular redness and itching when working with dogs
- she has a history of childhood asthma, but no recent symptoms
- no lower respiratory symptoms with dog exposure in the course of her work
- past allergic history includes mild seasonal allergic rhinitis controlled with antihistamines

Allergy Skin Tests

Dog dander	12 mm wheal
Tree	6 mm wheal
grass	8 mm wheal

Worksheet

Dog Prescription

Treatment set 1

Maintenance concentration final vial:

- Dog 5000 PNU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- Dog 2500 PNU

Explanation

Rationale for Immunotherapy	• We support the use of dog immunotherapy for occupational exposure, and this patient is a veterinary student • Though patient numbers are small, studies have shown the efficacy of dog immunotherapy at relatively high doses
Choice of Allergen(s)	• Dog • Her tree and grass symptoms are mild and well controlled with occasional antihistamines
Dosing	CSACI recommended prescription: • dog: 5000 PNU/ml • the 1:10 w/v product from ALK is equivalent to 20,000 PNU, which contains Can f 1 of 1-5 mcg/ml (more Can f 2, but not in the recommended dosing). • maintenance dose per 0.5 ml maintenance injection: ○ Dog: 2500 PNU Practice parameter: Effective dose range for dog is 15 mcg per 0.5 ml maintenance dose. • Using CSACI recommended dose would provide as little as 0.62 mcg Can f 1 per 0.5 ml maintenance injection, however that matches with previous wt/vol recommendations for safety—see Editorial note below.
Other considerations	• If the clinical response is inadequate, consider increasing the dose For non-occupational situations: • Most effective approach is dog avoidance • Reality is pets are not usually removed from the home.

Editorial note: Some members of the editorial board would prefer not to use dog for immunotherapy in Canada. The 2011 guideline recommended dose for dog is stated in mcg only. Guideline recommendation of 15 mcg Can f 1 cannot be achieved using the Canadian ALK product. This product has a relatively higher dose of Can f 2, which is not considered in the current potency calculation. The acetone precipitated Dog from Hollister-Stier is not available in Canada, and only the acetone precipitation is able to achieve such high content of Can f 1. For further discussion, see Smith: 2016 Annals Allergy¹⁶

¹⁶ D.M. Smith and C.A. Coop / Ann Allergy Asthma Immunol 116 (2016) 188-193

Problem 5

Patient History and Physical Examination

- an 18 year old student has a 3 year history of rhinoconjunctivitis symptoms beginning in mid-August and ending with the first frost
- he also has mild symptoms in the spring, but these are easily controlled with antihistamines over the spring season
- in the fall, there has not been any significant improvement with the regular use of anti-allergy eye drops and intranasal steroids
- a major symptom has been itching of the palate, not improved with antihistamines

Allergy Skin Tests

Tree mix	4 mm wheal
ragweed	9 mm wheal with pseudopods

Worksheet

Ragweed Prescription

Treatment set 1

Maintenance concentration final vial:

- ragweed 5000 PNU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- ragweed 2500 PNU
-

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinitis • Recommended medical treatment was not effective • Therefore reasonable to prescribe immunotherapy
Choice of Allergen(s)	• ragweed • Patient has significant symptoms of allergic rhinitis during the ragweed season, and a positive allergy skin test to ragweed • Symptoms in tree pollen season were well controlled with antihistamines, and so trees were not added
Dosing	CSACI recommended prescription: • ragweed 5000 PNU/ml • maintenance dose per 0.5 ml maintenance injection: ○ ragweed: 2500 PNU Practice parameter: Effective dose range for non-standardized allergens dosed in PNU (trees, ragweed) is 1000-4000 PNU per 0.5 ml maintenance dose • 2500 PNU per dose is midway in the effective dosing range
Other considerations	Alternate prescription: • Although the tree skin test was small, if this patient had more than just mild, easily controlled symptoms in the spring, immunotherapy to trees could be added to the ragweed prescription e.g.: Prescription: • ragweed 5000 PNU/ml • tree mix 5000 PNU/ml • Maintenance dose per 0.5 ml maintenance injection for: • tree Mix 2500 PNU • ragweed 2500 PNU

In this problem, and in others that follow, note that allergy skin testing and immunotherapy are sometimes done using a “tree mix,” instead of the individual trees. If a tree mix is used, some patients may be receiving immunotherapy for trees to which they are not allergic, hence the recommendation that individual trees be used for skin testing and desensitization. It is also important to know the specific trees contained in the particular tree mix you are using, and know that they are relevant to your geographic area.

Problem 6

Patient History and Physical Examination:

- a 55 year old man from Ontario has a 9 year history of significant rhinoconjunctivitis symptoms each May
- keeping the windows closed, and using regular antihistamine and intranasal steroids, were not effective in controlling his symptoms
- he also experiences oral itching and throat irritation after he eats raw apples and hazelnuts
- he would like to try allergen immunotherapy to treat the food related symptoms
- he has a history of hypertension and is on atenolol

Allergy Skin Tests

birch	10 mm wheal with pseudopods
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Worksheet

Birch Prescription

Treatment set 1

Maintenance concentration final vial:

- birch 5000 PNU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- birch 2500 PNU
-

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinoconjunctivitis • Recommended medical therapy was not effective • Therefore reasonable to prescribe immunotherapy
Choice of Allergen(s)	• birch • Patient's symptoms are timed with the birch season, to which he has a positive skin test • Note: beta-blockers are a contraindication to the use of allergen immunotherapy. Therefore, the beta-blocker should be changed to a non-beta blocker medication before this patient begins allergen immunotherapy
Dosing	CSACI recommended prescription: • birch 5000 PNU/ml • Maintenance dose per 0.5 ml maintenance injection: ○ birch 2500 PNU Practice parameter: Effective dose range for non-standardized allergens dosed in PNU (birch) is 1000-4000 PNU per 0.5 ml maintenance dose • 2500 PNU per dose is midway in the effective dosing range
Other considerations	• Symptoms of oral allergy syndrome have been very bothersome for this patient. • Studies (non-randomized controlled trials) suggest that immunotherapy with birch pollen may improve the symptoms of oral allergy syndrome

Problem 7

Patient History and Physical Examination

- a 14 year old boy has developed rhinoconjunctivitis symptoms starting mid-May through to the end of July
- he has tried various antihistamines, which were not tolerated because of sedation
- intranasal steroids and anti-allergy eye drops have provided some relief but he does not want to have to keep taking them on a regular basis
- his parents are concerned that his symptoms are more severe during the time of final examinations and may adversely affect his marks

Allergy Skin Tests

alder	2 mm wheal
birch	4 mm wheal
grass	10 mm wheal

Worksheet

Grass Prescription

Treatment set 1

Maintenance concentration final vial:

- grass 5000 BAU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- grass 2500 BAU
-

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of rhinoconjunctivitis • Recommended medical treatment has not resulted in clinical improvement, and he has experienced side effects with antihistamines • Therefore reasonable to prescribe immunotherapy
Choice of Allergen(s)	• Patient's symptoms are timed with the grass pollen season, to which he has a positive allergy skin test • Common grass pollens cross-react, hence grass mix is just as effective as individual grass allergens • Tree allergens were not added to the immunotherapy, since patient's symptoms only occurred during the grass season
Dosing	CSACI recommended prescription: • grass 5000 BAU/ml • grass is available as a standardized extract (BAU) in Canada • maintenance dose per 0.5 ml maintenance injection for: ○ grass 2500 BAU Practice parameter: Effective dose range for grass is 1000-4000 BAU per 0.5 ml maintenance dose • 2500 BAU is midway in the effective dosing range

Problem 8

Patient History and Physical Examination

- 37 year old female has a 20 year history of nasal congestion
- her symptoms have been seasonal and most troublesome in August and September
- she has not found any relief with over-the-counter antihistamines
- she has tried intranasal steroids daily for four months with approximately 50% improvement in the spring, but insufficient improvement in the fall, and significant impact on her quality of life
- she dislikes intranasal steroids, despite having tried several different preparations
- on nasal examination, the inferior turbinates are pale and congested

Allergy Skin Tests

ragweed	7 mm wheal
birch	5 mm wheal
grass mix	5 mm wheal

Worksheet

Ragweed, birch & grass prescription

Treatment set 1

Maintenance concentration final vial:

- ragweed 5000 PNU/ml
- birch 5000 PNU/ml
- grass 5000 BAU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose 0.5 ml/injection

- ragweed 2500 PNU
 - birch 2500 PNU
 - grass 2500 BAU
-

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinitis • Recommended medical therapy was not effective • Patient dislikes intranasal steroids • Therefore reasonable to prescribe immunotherapy
Choice of Allergen(s)	• birch, grass, ragweed • Patient has allergic rhinitis that is timed with the birch, grass, and ragweed seasons, and positive allergy skin tests to birch, mixed grass, and ragweed
Dosing	CSACI recommended prescription: • ragweed 5000 PNU/ml • birch 5000 PNU/ml • grass 5000 BAU/ml • maintenance dose for allergen(s) per 0.5 ml maintenance injection: ○ ragweed 2500 PNU ○ birch 2500 PNU ○ grass 2500 BAU Practice parameter: Effective dose range for non-standardized allergens dosed in PNU (birch, ragweed) is 1000-4000 PNU per 0.5 ml maintenance dose ○ 2500 PNU is midway in the effective dose range • Effective dose range for standardized grass is 1000-4000 BAU per 0.5 ml maintenance dose ○ 2500 BAU is midway in the effective dosing range

Problem 9

Patient History and Physical Examination

- a 17 year old male has a 5 year history of severe nasal congestion, sneezing and post nasal drip in the spring and fall
- his symptoms start in April, are better in July, then worsen in August
- at his worst he has trouble sleeping, and this past June he had trouble with exam performance
- he has tried “every antihistamine under the sun” but finds that they make him tired
- intranasal steroids help but he is still symptomatic and does not want to be “on them forever.”
- on examination nasal mucosa is pale and inferior nasal turbinates are edematous, conjunctivae are reddened and chest is clear.

Allergy Skin Tests

Tree mix	6 mm wheal
birch	7 mm wheal
beech	6 mm wheal
ash	6 mm wheal
ragweed	8 mm wheal

Worksheet

Birch, beech, ash & ragweed Prescription

Treatment set 1

Maintenance concentration final vial:

- birch 2500 PNU/ml
- ash 2500 PNU/ml
- ragweed 5000 PNU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- birch 1250 PNU
 - ash 1250 PNU (for a combined tree pollen dose of 2500 PNU)
 - ragweed 2500 PNU
-

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinitis • Recommended medical therapy was not effective • Patient dislikes intranasal steroids • Symptoms interfere with sleep and exam performance • Therefore reasonable to prescribe immunotherapy
Choice of Allergen(s)	• Birch, ash, ragweed • Patient has allergic rhinitis that is timed with the birch, beech, ash, and ragweed seasons, and positive allergy skin tests to birch, beech, ash, and ragweed • Birch, alder, and hazel cross react with beech, oak, chestnut • Choice is either birch or beech to cover both allergens • Ash does not cross react with birch or beech
Dosing	CSACI recommended prescription: • birch 2500 PNU/ml • ash 2500 PNU/ml • ragweed 5000 PNU/ml Maintenance dose per allergen(s) per 0.5 ml maintenance injection for: ○ birch 1250 PNU ○ ash 1250 PNU (for a combined tree pollen dose of 2500 PNU) ○ ragweed 2500 PNU Practice parameter: Effective dose range for non-standardized allergens dosed in PNU (birch, ash, ragweed) is 1000-4000 PNU per 0.5 ml maintenance dose • 2500 PNU is midway in the effective dose range

Ash is from the Oleaceae family, which does not cross react with the birch or beech.

Problem 10

Patient History and Physical Examination

- a 54-year old woman has a longstanding history of allergic rhinoconjunctivitis and mild asthma
- her symptoms are only present from spring to fall, and she is well in the winter
- her asthma is mild, with normal pulmonary function tests and she takes low dose inhaled steroid regularly
- she is intolerant of every intranasal steroid she has tried (six!) and dislikes antihistamines (she says even the “non-sedating” ones cause sedation)
- she uses topical decongestants once or twice a week. She has been instructed to discontinue this, but always reverts to using them during the summer to get some sleep.
- she has mild symptoms of oral allergy syndrome, mainly from uncooked apples and pears
- she has been having chest tightness that is triggered by exercise

Allergy Skin Tests

Tree mix	5 mm wheal
maple	3 mm wheal
birch	6 mm wheal
grass mix	10 mm wheal
ragweed	10 mm wheal
Alternaria	5 mm wheal
Cladosporium	10 mm wheal

Worksheet

Cladosporium, birch, grass & ragweed prescription

Treatment set 1	Treatment set 2
Maintenance concentration final vial • birch 5000 PNU/ml • grass 5000 BAU/ml	Maintenance concentration final vial • ragweed 5,000 PNU/ml • Cladosporium 5,000 PNU/ml
Number of dilutions: 4, Volume: 10 ml	Number of dilutions: 4, Volume: 10 ml
Final Maintenance Dose 0.5 ml/injection • birch 2500 PNU • grass 2500 BAU	Final Maintenance Dose 0.5 ml/injection, • ragweed 2500 PNU • Cladosporium 2500 PNU

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinoconjunctivitis and mild asthma • Intolerant of all intranasal steroids and antihistamines • Using topical decongestants • Avoidance measures for allergens ineffective • Therefore, reasonable to prescribe immunotherapy
Choice of Allergen(s)	• Birch, grass, ragweed, Cladosporium • Patient has allergic rhinitis from spring to fall primarily, timed with birch, grass, ragweed and Cladosporium season • Because of cross reactivity, treatment with either of Alternaria or Cladosporium or both would be equally acceptable • One could consider treating with a combination of tree pollens (tree mix), especially in North America where standardized birch pollen is not widely available, and other tree pollens are probably clinically relevant. • Grass pollen is sensitive to enzymatic degradation if mixed with mould. Ragweed will tolerate such a mixture, and has been chosen to mix with Cladosporium • Mould could be kept entirely separate in a third treatment set (extra cost and inconvenience)
Dosing	Practice parameter: Effective dose range for non-standardized allergens dosed in PNU (birch, ragweed) is 1000-4000 PNU per 0.5 ml maintenance dose • 2500 PNU is midway in the effective dose range • Effective dose range for grass is 1000-4000 BAU per 0.5 ml maintenance dose • 2500 BAU is midway in the effective dosing range Treatment set 2: CSACI recommended Cladosporium dose: 5000 PNU/ml • maintenance dose per 0.5ml maintenance injection: ◦ Cladosporium 2500 PNU Practice parameter: Effective dose range for Cladosporium is the

	“highest tolerated dose” per 0.5 ml maintenance dose which is impractical, hence CSACI recommendation is used • Aim for the lower end of the therapeutic range and adjust the dose downward if poorly tolerated or upward if poor efficacy after the first year Ragweed 5000 PNU/ml • maintenance dose per 0.5 ml maintenance injection for: ○ ragweed 2500 PNU Practice parameter: Effective dose ranges for non-standardized allergens dosed in PNU (ragweed) are 1000–4000 PNU/dose per 0.5 ml maintenance dose ○ 2500 PNU is midway in the effective dose range
Other considerations	• This patient has chest tightness triggered by exercise • Asthma, if present, must be controlled before immunotherapy is considered • <i>Angina and coronary artery disease must be ruled out before the patient starts allergen immunotherapy</i> • Any significant cardiac condition is a relative contraindication to receiving allergen immunotherapy (increased risk of severe and potentially life-threatening anaphylaxis if they have a reaction)

Problem 11

Patient History and Physical Examination

- a 26 year old woman has developed increasingly severe seasonal rhinoconjunctivitis in the past two years following the birth of her second child
- she has history of seasonal allergy in childhood, which disappeared after a five-year course of immunotherapy, completed at about age 13
- her symptoms are significant in May and early June and at their worst in late August through September
- she finds them quite incapacitating at times and has only partial relief with regular intranasal steroids, anti-allergy eye drops, and oral antihistamines
- she has no formal history of asthma however has begun to notice some shortness of breath and occasional wheezing primarily in August and September, but also continuing into October and November, and in high humidity

Allergy Skin Tests

Alternaria	12 mm wheal
birch	16 mm wheal
ragweed	18 mm wheal

- No significant reactions to any other moulds, tree pollens, or grass pollen

Worksheet

Alternaria, birch & ragweed prescription

Treatment set 1	Treatment set 2
Maintenance Concentration Final Vial • birch 5000 PNU/ml • ragweed 5000 PNU/ml	Maintenance Concentration Final Vial • Alternaria 5000 PNU/ml
Number of dilutions: 4, Volume: 10 ml	Number of dilutions: 4, Volume: 10 ml
Final maintenance dose: 0.5 ml/injection • birch 2500 PNU • ragweed 2500 PNU	Final maintenance dose 0.5 ml/injection • Alternaria 2500 PNU

Explanation

Rationale for Immunotherapy	• Patient has significant symptoms of allergic rhinoconjunctivitis • Recommended medical therapy was only partially effective • Good response to previous immunotherapy • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• birch, ragweed, and Alternaria • Patient's worst symptoms of allergic rhinitis and probable asthma are timed with the birch, ragweed, and Alternaria seasons to which he has positive skin tests • Though birch is the only positive skin test, use of a tree mix could be considered if skin tests were positive to more trees and those tests were positive in tree families that did not cross-react
Dosing	CSACI recommended prescription treatment set 1: • birch 5000 PNU/ml • ragweed 5000 PNU/ml • Maintenance dose per allergen per 0.5 ml maintenance injection for: ○ birch 2500 PNU ○ ragweed 2500 PNU • Practice parameter: Effective dose ranges for non-standardized allergens dosed in PNU (birch, ragweed) are 1000–4000 PNU/dose per 0.5 ml maintenance dose • 2500 PNU is midway in the effective dose range CSACI recommended prescription treatment set 2: • Alternaria: 5000 PNU/ml • Maintenance dose per 0.5 ml maintenance injection for: ○ Alternaria: 2500 PNU ○ 2500 PNU is midway in the effective dose range • Practice parameter: Effective dose range for Alternaria is the “highest tolerated dose” per 0.5 ml maintenance dose which is impractical, hence CSACI recommendation of 5000 PNU/ml is used • ragweed and birch can be mixed because neither has significant enzymatic activity • Alternaria should be separate from birch as it has enzymatic activity which may affect the potency of the birch allergen

Problem 12

Patient History and Physical Examination

- a 38 year old man marries a woman with a dog and moves into her apartment
- shortly after, he develops significant ocular symptoms, rhinorrhea and cough
- his symptoms improve markedly when travelling for work as an Air Canada pilot
- sedating antihistamines work, but he can't take them because of his job
- his nose is too dry for an intranasal steroid, and a trial of a leukotriene antagonist failed

Allergy Skin Test

D. farinae	6 mm wheal
D. pteronyssinus	5 mm wheal
Cat	6 mm wheal
Dog	5 mm wheal

Worksheet

House dust mite, cat & dog prescription

Treatment set 1	Treatment set 2
Maintenance concentration final vial • D. farinae 1000 AU/ml • D. pteronyssinus 1000AU/ml	Maintenance Concentration Final Vial • cat 2000 BAU/ml • dog 5000 PNU/ml
Number of dilutions: 4, Volume: 10 ml	Number of dilutions: 4, Volume: 10 ml
Final Maintenance Dose 0.5 ml/injection: • D. farinae 500 AU • D. pteronyssinus 500 AU	Final Maintenance Dose 0.5 ml/injection • cat 1000 BAU • dog 2500 PNU

Explanation

Rationale for Immunotherapy	• Patient has significant and persistent symptoms of allergic rhinoconjunctivitis • Because of his profession as a pilot, he cannot take sedating antihistamines which he claims are the only ones that work • Intranasal steroids have led to side effects • Leukotriene receptor antagonists did not work • Generally, we would prefer to have pet avoidance before starting immunotherapy, however the dog will likely not be given away, and animal allergens are not generally encountered at work • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• House dust mites-D farinae (Der f 1) and D pteronyssinus (Der p 1), cat, dog • Though patient numbers are small, studies have shown the efficacy of dog immunotherapy. • Cat immunotherapy has also shown efficacy in studies where the patient does not own cats
Dosing	CSACI recommended prescription #1: • Der p 1 and Der f 1 2000 AU/ml per allergen • Because of significant cross-reactivity between Der p 1 and Der f 1, 1000 AU/ml per allergen has been prescribed • Maintenance dose per 0.5 ml maintenance injection: ○ 500 AU for each of Der p 1 and Der f 1 or 1000 AU total per dose • Practice parameter: Effective dose range for Der p 1 is 7-12 mcg and for Der f 1 is 10 mcg. This is in the range of 500-2000 AU per 0.5 ml maintenance dose ○ The combined 1000 AU/dose is at the lower end of the effective dosing range. CSACI recommended prescription #2: • cat: 2000 BAU/ml • dog: 5000 PNU/ml • Maintenance dose per 0.5 ml maintenance injection: ○ cat: 1000 BAU ○ dog: 2500 PNU

	Practice parameter: Effective dose range for cat is 1000–4000 BAU per 0.5 ml maintenance dose CSACI recommendation: dog 5000 PNU/ml, 2500 PNU/dose Practice parameter: • Effective dose range for dog is 15 mcg per 0.5 ml maintenance dose. The 1:10 w/v product from ALK is equivalent to 20,000 PNU, which contains Can f 1 of 1-5 mcg/ml (more Can f 2, but not considered in the recommended dosing). • CSACI recommendation using Canadian products would provide as little as 0.62 mcg Can f 1 per 0.5 ml maintenance injection, however that seems to be effective, and matches with previous recommendations. Aim for the low end of the therapeutic range, and adjust upward after 1 year if it is not effective
Other considerations	• Current guidelines suggest: “dust mite extracts do not appear to have a deleterious effect on pollen extracts. These studies suggest that pollen, dust mite, and cat extracts can be mixed together”

Editorial note: Some members of the editorial board would prefer not to use dog for immunotherapy in Canada. The 2011 guideline recommended dose for dog is stated in mcg only. Guideline recommendation of 15 mcg Can f 1 cannot be achieved using the Canadian ALK product. This product has a relatively higher dose of Can f 2, which is not considered in the current potency calculation. The acetone precipitated Dog from Hollister-Stier is not available in Canada, and only the acetone precipitation is able to achieve such high content of Can f 1. For further discussion, see Smith: 2016 Annals Allergy¹⁷

¹⁷ D.M. Smith and C.A. Coop / Ann Allergy Asthma Immunol 116 (2016) 188-193

Problem 13

Patient History and Physical Examination

- a 23 year old woman, living in Vancouver for the past 3 years, has perennial rhinoconjunctivitis symptoms with seasonal exacerbations during the months of February, March, and April and again in September and early October
- she is hesitant about using any medications regularly, although she notes that the occasional use of antihistamines has provided some symptomatic relief
- she does not want to use intranasal steroids

Allergy Skin Tests

D. farinae	8 mm wheal
D. pteronyssinus	6 mm wheal
Alternaria	6 mm wheal
Red alder	10 mm wheal
birch	5 mm wheal

Worksheet

House dust mite, Alternaria & alder prescription

Treatment set 1	Treatment set 2
Maintenance concentration final vial: • D. farinae: 1000 AU/ml • D. pteronyssinus 1000 AU/ml • Alternaria 5000 PNU ml	Maintenance dose final vial: • birch 2500 PNU/ml • alder 2500 PNU/ml
Number of dilutions: 4, Volume: 10 ml	Number of dilutions: 4, Volume: 10 ml
Final maintenance Dose: 0.5 ml/injection • D. pteronyssinus 500 AU • D. farinae 500 AU • Alternaria 2500 PNU	Final maintenance dose: 0.5 ml/injection • birch 1250 PNU • alder 1250 PNU

Explanation

Rationale for Immunotherapy	• Patient has persistent symptoms of allergic rhinoconjunctivitis • Does not want to use regular antihistamines or intranasal steroids • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• House dust mites, birch, alder and Alternaria • Patient has year round symptoms secondary to House dust mites, with worsening in the spring and fall, secondary to tree and Alternaria allergy, with positive skin tests to house dust mites, birch, alder, and Alternaria • Alternaria spores tend to rise in the late summer and early fall months • Early spring allergies are most likely related to alder, although there is significant cross-reactivity with birch (Betulaceae family) • Mixing mould with the tree pollens is not recommended because the high protease activity in the mould could break down tree pollens
Dosing	CSACI recommended prescription treatment set 1: • Der p 1 and Der f 1: 2000 AU/ml per allergen • Because of significant cross-reactivity between Der p 1 and Der f 1, 1000 AU/ml per allergen has been prescribed • Maintenance dose per 0.5 ml maintenance injection: ○ 500 AU for each of Der p 1 and Der f 1 or 1000 AU total per dose Practice parameter: Effective dose range for Der p 1 is 7-12 mcg and for Der f 1 is 10 mcg. This is in the range of 500-2000 AU per 0.5 ml maintenance dose ○ The combined 1000 AU/dose is at the lower end of the effective dosing range. • Alternaria: 5000 PNU/ml • Maintenance dose per 0.5ml maintenance injection for: ○ Alternaria: 2500 PNU Practice parameter: Effective dose range for Alternaria is the “highest tolerated dose” per 0.5 ml maintenance dose which is impractical,

	hence the CSACI recommendation is used CSACI recommended prescription treatment set 2: • birch 5000 PNU/ml • alder 5000 PNU/ml • maintenance dose per allergen per 0.5 ml maintenance injection: ○ birch 2500 PNU ○ alder 2500 PNU Practice parameter: Effective dose ranges for non-standardized allergens dosed in PNU (birch, alder) are 1000–4000 PNU/dose per 0.5 ml maintenance dose ○ 2500 PNU is midway in the effective dose range Alternate prescription: <i>We elected to use both alder and birch pollen. Since the birch and alder are in the same family, it would be equally acceptable to choose either ONE of these using a dose of 5000 PNU/ml (e.g. 2500 PNU per final maintenance dose)</i>
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Problem 14

Patient History and Physical Examination

- a 12 year old girl from Southern Ontario has had severe symptoms of nasal stuffiness, sneezing and itchy red eyes from mid-August to the first frost
- the symptoms have occurred even with the use of intranasal steroids, antihistamines, anti-allergy eye drops and a leukotriene antagonist
- both she and her parents would like her to try immunotherapy
- her mother states that she herself was on immunotherapy as a child, and her symptoms “disappeared”

Allergy Skin Tests

ragweed	8 mm wheal
Cladosporium	10 mm wheal

- No significant reaction to other moulds tested (*Alternaria*, *Aspergillus*, *Penicillium*)

Worksheet

Cladosporium & ragweed prescription

Treatment set 1

Maintenance concentration final vial:

- ragweed 5000 PNU/ml
- Cladosporium 5000 PNU/ml

Number of dilutions: 4, Volume: 10 ml

Final maintenance Dose: 0.5 ml/injection

- ragweed 2500 PNU
 - Cladosporium 2500 PNU
-

Explanation

Rationale for Immunotherapy	• Young patient has severe rhinoconjunctivitis • Recommended medical therapy has not been effective • Patient and parents want her to try immunotherapy • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• ragweed, Cladosporium • Symptoms are severe from mid-August to first frost, and are timed with ragweed and Cladosporium seasons, to which she has positive skin tests
Dosing	CSACI recommended prescription: • ragweed: 5000 PNU/ml • maintenance dose per 0.5 ml maintenance injection for: ○ ragweed: 2500 PNU Practice parameter: Effective dose range for non-standardized allergens dosed in PNU (ragweed) is 1000-4000 PNU per 0.5 ml maintenance dose. ○ 2500 PNU per dose is midway in the effective dosing range CSACI recommended prescription: • Cladosporium: 5000 PNU/ml • maintenance dose per 0.5ml maintenance injection for: ○ Cladosporium: 2500 PNU Practice parameter: Effective dose range for Cladosporium is the “highest tolerated dose” per 0.5 ml maintenance dose which is impractical, hence the CSACI recommendation is used • ragweed and Cladosporium can be mixed in one vial. Although Cladosporium has proteases that can break down pollen allergens, ragweed is more resistant to these enzymes
Other considerations	• If patient only had ragweed identified as the cause of symptoms, pre-seasonal ragweed immunotherapy could be considered

Problem 15

Patient History and Physical Examination

- a 32 year old female on the West Coast has symptoms of perennial rhinoconjunctivitis with seasonal worsening from spring to fall
- this has been troublesome for the past three to four years
- the regular use of an over-the-counter antihistamine, intranasal steroids and anti-allergy eye drops have failed to control her symptoms

Allergy Skin Tests

D. farinae	6 mm wheal
D. pteronyssinus	5 mm wheal
alder	7 mm wheal
grass mix	10 mm wheal
ragweed	8 mm wheal

Worksheet

House dust mite, alder, grass & ragweed prescription

Treatment set 1	Treatment set 2
Maintenance concentration final vial • D. farinae 1000AU/ml • D. pteronyssinus 1000AU/ml	Maintenance Concentration Final Vial • alder 5000 PNU/ml • grass 5000 BAU/ml • ragweed 5000 PNU/ml
Number of dilutions: 4, Volume: 10 ml	Number of dilutions: 4, Volume: 10 ml
Final Maintenance Dose 0.5 ml/injection: • D. farinae 500 AU • D. pteronyssinus 500 AU	Final Maintenance Dose 0.5 ml/injection • alder 2500 PNU • grass 2500 BAU • ragweed 2500 PNU

Explanation

Rationale for Immunotherapy	• Patient has persistent symptoms of rhinitis with worsening from spring to fall • Recommended medical therapy was not effective • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• House dust mites, alder, grass and ragweed • Patient has persistent symptoms of rhinitis consistent with allergy to house dust mites, with worsening from spring to fall, timed with tree, grass, and ragweed seasons, to which she has positive skin tests.
Dosing	CSACI recommended prescription treatment set 1: • Der p 1 and Der f 1: 2000 AU/ml per allergen • because of significant cross-reactivity between Der p 1 and Der f 1, 1000 AU/ml per allergen has been prescribed • maintenance dose per 0.5 ml maintenance injection: ○ 500 AU for each of Der p 1 and Der f 1 or 1000 AU total per dose Practice parameter: Effective dose range for Der p 1 is 7-12 mcg and for Der f 1 is 10 mcg. This is in the range of 500-2000 AU per 0.5 ml maintenance dose ○ The combined 1000 AU/dose is at the lower end of the effective dosing range CSACI recommended prescription treatment set 2: • alder 5000 PNU/ml • ragweed 5000 PNU/ml • maintenance dose per 0.5 ml maintenance injection: ○ alder: 2500 PNU ○ ragweed: 2500 PNU Practice parameter: Effective dose ranges for non-standardized allergens dosed in PNU (alder, ragweed) are 1000–4000 PNU/dose per 0.5 ml maintenance dose ○ 2500 PNU is midway in the effective dose range CSACI recommended prescription:

	• grass: 5000 BAU/ml • Maintenance dose per 0.5 ml maintenance injection: ○ grass: 2500 BAU Practice parameter: grass is available as a standardized allergen in BAU. Effective dose range is 1000–4000 BAU per 0.5 ml maintenance dose ○ 2500 BAU per dose is midway in the effective dosing range
Other considerations	It would be acceptable to put all allergens in the same treatment vial since they all have low protease activity

Problem 16

Patient History and Physical Examination

- an 18 year old female with severe allergic rhinitis and moderate asthma, has frequent asthma exacerbations in summer and fall for the past 8 years
- she sleeps in the basement with wall to wall carpets
- antihistamines and intranasal steroids have not improved her symptoms
- the patient is taking a combination asthma inhaler
- she admits that she is not using it regularly and has had one emergency visit for asthma eight months ago
- she would like to try allergen immunotherapy
- her physical examination revealed edema of the nasal mucosa, and wheezing
- her pulmonary function test revealed an FEV1 78% predicted (20% reversibility)

Allergy Skin Tests

D. farinae	10 mm wheal
D. pteronyssinus	15 mm wheal
grasses	20 mm wheal
Alternaria	10 mm wheal
Cladosporium	10 mm wheal

Worksheet

Alternaria, Cladosporium & house dust mites prescription

Treatment set 1	Treatment set 2
Maintenance concentration final vial • D. farinae 1000 AU/ml • D. pteronyssinus 1000 AU/ml	Maintenance Concentration Final Vial • Alternaria 2500 PNU/ml • Cladosporium 2500 PNU/ml • ragweed 5000 PNU/ml
Number of dilutions: 4, Volume: 10 ml	Number of dilutions: 4, Volume: 10 ml
Final Maintenance Dose 0.5 ml/injection: • D. farinae 500 AU • D. pteronyssinus 500 AU	Final Maintenance Dose 0.5 ml/injection • Alternaria 1250 PNU • Cladosporium 1250 PNU • ragweed 2500 PNU

Explanation

Rationale for Immunotherapy	• Patient has persistent severe allergic rhinitis symptoms • Recommended medical therapy has not been effective • Moderate asthma which exacerbates in the summer and fall • She is not compliant with asthma therapy and has had an emergency visit recently • Pulmonary function shows an FEV1 of 78% predicted and 20% response to bronchodilator • Her asthma is not well controlled which is a contraindication to immunotherapy. She was advised to use her combination inhaler at two inhalations twice per day After one month of treatment: • Asthma symptoms resolved and the FEV1 improved by 15% • No longer showing reversibility after bronchodilator. • Still having allergic rhinitis symptoms • With improvement of her asthma and asthma education, it is reasonable to prescribe immunotherapy, with careful monitoring
Choice of Allergen(s)	• House dust mites, Alternaria, Cladosporium, and ragweed

Dosing	CSACI recommended prescription treatment set 1: • Der p 1 and Der f 1: 2000 AU/ml per allergen • Because of significant cross-reactivity between Der p 1 and Der f 1, 1000 AU/ml per allergen has been prescribed • Maintenance dose per 0.5 ml maintenance injection: ○ 500 AU for each of Der p 1 and Der f 1 or 1000 AU total per dose Practice parameter: Effective dose range for Der p 1 is 7-12 mcg and for Der f 1 is 10 mcg. This is in the range of 500-2000 AU per 0.5 ml maintenance dose ○ The combined 1000 AU/dose is at the lower end of the effective dosing range. CSACI recommended prescription treatment set 2: • Alternaria: 2500 PNU/ml • Cladosporium: 2500 PNU/ml • Maintenance dose per 0.5 ml maintenance injection for: ○ Alternaria: 1250 PNU ○ Cladosporium: 1250 PNU • because of cross reactivity between Alternaria and Cladosporium, it is appropriate to prescribe 1250 PNU of each allergen to a total of 2500 PNU/ml ○ 2500 total PNU is midway in the effective dose range for mould Practice parameter: Effective dose range for Alternaria or Cladosporium is the “highest tolerated dose” per 0.5 ml maintenance dose which is impractical, hence CSACI recommendation is used • ragweed 5000 PNU/ml • maintenance dose per 0.5 ml maintenance injection: ○ ragweed: 2500 PNU Practice parameter: Effective dose ranges for non-standardized allergens dosed in PNU (ragweed) are 1000–4000 PNU/dose per 0.5 ml maintenance dose ○ 2500 PNU is midway in the effective dose range • <i>NB:</i> House dust mites, ragweed, and moulds can be mixed in one vial as the proteases in the moulds do not break down these other allergens significantly.
Other considerations	• Patient must be given clear instructions that her asthma must be well controlled on regular inhaler therapy, and that she not receive an injection if she is symptomatic from her asthma • Asthma must be assessed at the time of every injection

Problem 17

- 42 year old man has a history of troublesome springtime allergic rhinoconjunctivitis for the past several years.
- adequate medical therapy has not been sufficient to control the symptoms, which are now interfering with work and sports.
- the referring physician has suggested immunotherapy, and the patient is very interested.

Allergy Skin Tests

grass	8 mm wheal
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You would like to offer him regular subcutaneous immunotherapy, but it is now February by the time you see him in consultation, and there isn't enough time for regular subcutaneous immunotherapy.

Worksheet

Pre-seasonal grass allergen immunotherapy prescription

Treatment set 1 (example: Centre-AI)

For example, Centre-AI grass immunotherapy

9 injections, one week apart, to begin immediately

Injections should be completed 1–2 months prior to the season

3 vial set: (50 PNU, 500 PNU, 5000 PNU)

Final maintenance Dose: 0.3 ml/injection

- Alum precipitated grass 1500 PNU/inj

Explanation

Rationale for Immunotherapy	• History of troublesome allergic rhinoconjunctivitis in the spring • Recommended medical therapy has not been effective
Choice of Allergen(s)	• grass
Dosing	• Patient's symptoms are in the spring, timed with grass pollen season to which he has a positive skin test • Pre-seasonal therapy to grass is appropriate since it is too late (February) to start year round immunotherapy • The main benefit of pre-seasonal injections is the reduced number of doses required to reach maintenance, which allows this to be used as a pre-seasonal product • They are alum-precipitated which result in a slower, more prolonged release of the allergen. • This pre-seasonal injection would need to be re-administered the following year, for several consecutive years
Other considerations	• There is large variability in the dosing schedule for the different pre-seasonal grass pollen products

There are several manufacturers in Canada including Allergy Canada, and "Suspal" (Omega).

Centre-AI				Allergy Canada				Omega "Suspal"			
Vial Number	Dose	Amount	Total PNU/inj	Vial Number	Dose	Amount	Total PNU/inj	Vial Number	Dose	Amount	Total PNU/inj
1 (50 PNU/ml)	1	0.1 ml	5	1 (1,000 PNU/ml)	1	0.15 ml	150	1 (500 PNU/ml)	1	0.1 ml	50
	2	0.2 ml	10		2	0.3 ml	300		2	0.2 ml	100
	3	0.3 ml	15		3	0.6 ml	600		3	0.4 ml	200
2 (500 PNU/ml)	4	0.1 ml	50	2 (10,000 PNU/ml)	4	0.1 ml	1000	2 (5,000 PNU/ml)	4	0.1 ml	500
	5	0.2 ml	100		5	0.15 ml	1500		5	0.2 ml	1000
	6	0.3 ml	150		6	0.25 ml	2500		6	0.4 ml	2000
3 (5,000 PNU/ml)	7	0.1 ml	500		7	0.4 ml	4000		7	0.6 ml	3000
	8	0.2 ml	1,000						8	0.6 ml	3000
	9	0.3 ml	1,500						9	0.6 ml	3000

Problem 17a

- 35 year old woman
- ten year history of incapacitating rhinitis in the spring.
- works as an inspector for nuclear reactors, and travels the country for her job, and for her sport—she does roller derby.
- because of the travelling, she has refused perennial immunotherapy, and even pre-seasonal is extremely difficult as she is not home for any extended period of time to receive the injections.

Allergy Skin Tests

grass	6 mm wheal
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Worksheet

Grass SLIT-tablet prescription

Option 1: Oralair (Stallergenes)

Start tablets ideally four months before the expected grass season, minimum two months. The first tablet must be taken in the allergist's office, with 30 minutes of observation after the first tablet. The start-up kits are available from the manufacturer for the first few days, as follows.

Day 1: 1 x 100 IR tablet
Day 2: 2 x 100 IR tablets
Day 3: 1 x 300 IR tablet

The prescription must be written for the remainder as:

Rx: Oralair 300 IR tablets. Dispense 30. Refill 5. First tablet to be taken in the allergy clinic under observation. (It can also be dispensed for 2 or 3 months at a time with the appropriate number of repeats).

Option 2: Grastek (ALK)

Start tablets ideally three months before the expected grass season (range 2-4 months before). The first tablet must be taken in the allergist's office, with 30 minutes of observation after the first tablet. Start-up kits are available from the manufacturer, after which a prescription is written as:

Rx: Grastek tablets 2800 BAU. Dispense 30. Refill 5. First tablet to be taken in the allergy clinic under observation. (It can also be dispensed for 2 or 3 months at a time with the appropriate number of repeats).

Explanation

Rationale for Immunotherapy	• Ideal candidate for sublingual immunotherapy tablets (SLIT-T) • Patient cannot attend the multiple doctor visits required for injection therapy • Other good candidates include adults or children with needle phobia. • There is very little data to compare the efficacy of regular subcutaneous immunotherapy (or pre-seasonal subcutaneous immunotherapy) and SLIT • In general, the effect size (benefit) appears larger with subcutaneous
Choice of Allergen(s)	• Two choices of grass SLIT-T at this time: Grastek (ALK), and Oralair (Stallergenes)
Dosing	• Dosing of these two tablets is not directly comparable because of different units, but both represent a similar quantity of pollen in each daily tablet as is generally used for a monthly maintenance injection of aqueous immunotherapy • Oralair is a mixture of five different grass allergens, indicated for the treatment of grass pollen allergic rhinitis with or without allergic conjunctivitis in people 5 to 50 years of age. The manufacturer recommends that Oralair be started 4

	months prior to the grass pollen season and taken every day until the grass pollen season is over (generally a 6 month course) • Grastek is a single allergen tablet containing only Timothy grass pollen, indicated for the treatment of grass pollen allergic rhinitis with or without allergic conjunctivitis in people 5 to 65 years of age. The manufacturer recommends that Grastek be started at least 12 weeks prior to the grass pollen season and taken every day until the grass pollen season is over (generally a 6 month course) • Tablets would be re-started each year before the grass pollen season begins, with the first dose under medical supervision every year
Other considerations	• Common side effects of both tablets include: throat irritation and swelling, mouth and ear itching, and coughing. Most of these side effects have been mild, but approximately 0.1–0.4% of people have experienced a reaction severe enough to stop treatment. Anaphylaxis is far less likely than with subcutaneous immunotherapy • There is some evidence for both tablets, that when taken for at least three seasons (with Grastek, when taken throughout the year for three years), that there is a durable response lasting at least a year or two after stopping treatment. For this reason, patients, after discussion with their allergist, may choose to take either type of tablet daily throughout the year, and at least for a three year period

Problem 18

Patient History and Physical Examination

- 38 year old female with severe allergic rhinitis symptoms from mid-August to October
- she has tried intranasal steroids and antihistamines without significant improvement
- she has had symptoms for 4 years
- physical examination was normal

Allergy Skin Tests

birch	4 mm wheal
ragweed	6 mm wheal

Worksheet

Pre-seasonal ragweed Prescription

- Pollinex-R to be started in June
- Four injections in total, given as one injection weekly
- Top dose 2150 PNU in 0.5 ml

Explanation

Rationale for Immunotherapy	• Patient has severe symptoms of allergic rhinitis from mid-August to October • Recommended medical therapy has not been effective										
Choice of Allergen(s)	• ragweed										
Dosing	• This patient has symptoms timed with ragweed season, to which she has a positive skin test • Pollinex-R is a pre-seasonal immunotherapy that has been available to treat ragweed allergy for several decades • Pollinex-R is modified by glutaraldehyde and then adsorbed to tyrosine • Glutaraldehyde is used to modify the ragweed allergen so that it retains its immunogenicity, but is less likely to cause anaphylaxis • Tyrosine is adsorbed to the ragweed allergen so that it is released slowly, again decreasing the risk of anaphylaxis • Pollinex-R is administered in four injections given weekly, ideally in June, with a relatively rapid increase in dosing • Injections are supplied in prefilled syringes, in the following manner:<table><tr><th>Syringe Number</th><th>Strength in PNU per 0.5 ml</th></tr><tr><td>1</td><td>105</td></tr><tr><td>2</td><td>250</td></tr><tr><td>3</td><td>700</td></tr><tr><td>4</td><td>2150</td></tr></table> • In general, the Pollinex-R would be repeated each year for a number of years • NB: Alum precipitated ragweed extracts are also available for short course pre-seasonal immunotherapy. These are less expensive than Pollinex-R, but require more injections (typically 7-9)	Syringe Number	Strength in PNU per 0.5 ml	1	105	2	250	3	700	4	2150
Syringe Number	Strength in PNU per 0.5 ml										
1	105										
2	250										
3	700										
4	2150										

Problem 18a

- 18 year old male
- severe rhinoconjunctivitis in August and September for past 2 years
- interferes with sleep and summer soccer
- he dislikes intranasal steroids and was non-compliant
- antihistamines were not helpful
- injections were previously suggested but he is extremely needle-phobic and refused

Allergy Skin Tests

ragweed	9 mm wheal
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Worksheet

Prescription

- Pre-seasonal sublingual ragweed tablets: Ragwitek® (ALK)
- Start tablets ideally at least 12 weeks before the expected ragweed season.
- As with grass SLIT-T, the first tablet must be taken in the allergists office, with 30 minutes of observation after the first tablet.
- Start up kits are available from the manufacturer, after which a prescription is written as:

Rx: Ragwitek® 12 Amb a 1-Units (main ragweed allergen). Dispense 30. Refill 5. First tablet to be taken in the allergy clinic under observation. It can also be dispensed for 2 or 3 months at a time, with the appropriate number of repeats.

Explanation

Rationale for Immunotherapy	• Patient has severe rhinoconjunctivitis in August and September for the past 2 years • Recommended medical therapy has been ineffective, and she has been non compliant • Extremely needle phobic • Reasonable to prescribe immunotherapy
Choice of Allergen(s)	• ragweed
Dosing	• Patient has symptoms which are timed with the ragweed pollen season, to which she has a positive skin test • SLIT-T is an ideal choice for this patient • Ragwitek® is a single allergen tablet containing short ragweed pollen only, and is indicated for the treatment of ragweed pollen allergy associated allergic rhinitis with or without allergic conjunctivitis in people 18 to 65 years of age • Manufacturer recommends Ragwitek® be started at least 12 weeks prior to the ragweed pollen season and taken every day until the ragweed pollen season is over (generally 6 months, the same as for grass pollen SLIT-T) • Ragwitek® does need to be restarted yearly for the next few years if used for a 6 month duration • It can also be taken daily for at least a 3 year period, which is more expensive but possibly immunomodulatory, and may eliminate the need to re-start after the 3 year period.
Other considerations	• Side effect profile is similar to grass SLIT-T

Hymenoptera venom immunotherapy

Problem 19

Patient History

- 32 year old female amateur bee-keeper was stung on the back of the neck
- within 5 minutes, she had itching of her hands and soles of her feet
- within 10 minutes, there were generalized hives and chest tightness
- she drove to the emergency department, where she received epinephrine, salbutamol and diphenhydramine

Venom Skin Tests

	0.1 mcg/ml intradermal	1 mcg/ml intradermal
Honeybee	5 mm wheal	8 mm wheal/
Yellow jacket	Negative	Negative
Yellow hornet	Negative	Negative
White-faced hornet	Negative	Negative
Wasp	Negative	Negative

Worksheet

Honey bee prescription

- single venom immunotherapy with honey bee venom
- start at 0.1 ml of a 0.01 mcg/ml solution increasing according to product monograph standard schedule to a maintenance dose of honey bee 1 ml of a 100 mcg/ml solution
- after the build up dosing is completed, the injection interval is usually increased to monthly
- the immunotherapy is typically continued for 5 years

Explanation

Rationale for Immunotherapy	• Patient had a reaction to a honeybee sting consistent with anaphylaxis • He is a beekeeper
Choice of Allergen(s)	• Honeybee
Dosing	• Patient had a severe allergic reaction after a Honeybee sting, to which he has a positive skin test • Standard dosing for Honeybee immunotherapy is 100 mcg administered as a 100 mcg/ml injection monthly • Some data suggests that the interval can be increased to every two or three months, but the standard treatment interval is monthly • Immunotherapy should be continued for at least three years. If the skin test becomes negative, it can be stopped • If the skin testing remains positive at 3 years, the immunotherapy should be continued for at least 5 years.
Other considerations	• Because this patient is working as a beekeeper, an epinephrine auto-injector was prescribed • Many allergists use a variation (often abbreviated) of the product monograph for build-up scheduling

Problem 20

Patient History

- 36 year old male was stung on right hand while barbecuing at his house
- he did not see the stinging insect, but the sting was painful
- in 10 minutes, he developed wheezing, dyspnea, rhinoconjunctivitis and angioedema of the lips
- there was a transient loss of consciousness
- 911 was called and the paramedics treated him with two doses of epinephrine

Venom Skin Tests

	0.1 mcg/ml intradermal	1 mcg/ml intradermal
Honeybee	Negative	Negative
Yellow jacket	24 mm wheal	Not done
Yellow hornet	18 mm wheal	Not done
White-faced hornet	18 mm wheal	Not done
Wasp	Negative	Negative

Worksheet

Yellow jacket prescription

- venom immunotherapy with yellow jacket
- start at 0.1 ml of a 0.01 mcg/ml solution increasing according to product monograph standard schedule to a maintenance dose of 1 ml of a 100mcg/ml solution for yellow jacket
- after the maintenance dose is reached, the injection interval can be increased to monthly
- given the severity of the reaction, life-long immunotherapy was recommended
- injectable epinephrine should be carried

Explanation

Rationale for Immunotherapy	• Patient had a life-threatening anaphylactic reaction to a sting from an unidentified insect • NB: Current guidelines are under revision with respect to generalized cutaneous reactions—while this has been an indication for venom immunotherapy in the past, it has been removed from the Draft guidelines: please review when published.
Choice of Allergen(s)	• Yellow Jacket which because of cross reactivity will also protect against allergy to the hornets • Patient had anaphylaxis to an unidentified insect sting and positive skin tests to Yellow Jacket, Yellow and White-faced Hornets
Dosing	• Maintenance dosing for Yellow Jacket immunotherapy is 100 mcg administered as a 100 mcg/ml injection monthly
Other considerations	• In the opinion of some authors, if the insect can be clearly identified, the venom immunotherapy need only contain that specific venom • Other authors recommend that the extract contain venoms from all insects to the patient had positive skin tests (mixed vespid with a maintenance dose of 300mcg administered as a 300mcg/ml injection monthly) • For this patient, life-long immunotherapy may be recommended because of the severity of the reaction. • Many allergists use a variation (often abbreviated) of the product monograph for build-up scheduling • Serum tryptase can be ordered since severe allergic reactions to stinging insects may be the first presentation of systemic mastocytosis

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Appendix: Sample Dosing Schedule

DOSAGE SCHEDULE FOR IMMUNOTHERAPY EXTRACT / VACCINE

DR. _____

Address _____

Phone/Fax _____

AQUEOUS EXTRACT
SUGGESTED DOSAGE CHART

SCHEDULE FOR DESENSITIZATION

DR. _____ PATIENT _____ CONTENT: _____
LOT NO. _____ EXPIRY DATE _____

This is a suggested dose chart only. Please read the instructions before commencing desensitization.
Observe patients for 30 minutes after each injection.
Check extract dilution and dose - Check the patient for local or systemic reaction(s) to previous injection.

VIAL #1 1 :1000 (white)		VIAL #2 1 :100 (green)		VIAL #3 1 :10 (yellow)		VIAL #4 1 :1 (red)	
DOSE	DOSAGE	DOSE	DOSAGE	DOSE	DOSAGE	DOSE	DOSAGE
1	0.1 cc	6	0.1 cc	11	0.1 cc	16	0.05 cc
2	0.2 cc	7	0.2 cc	12	0.2 cc	17	0.07 cc
3	0.3 cc	8	0.3 cc	13	0.3 cc	18	0.10 cc
4	0.4 cc	9	0.4 cc	14	0.4 cc	19	0.15 cc
5	0.5 cc	10	0.5 cc	15	0.5 cc	20	0.20 cc
						21	0.25 cc
						22	0.30 cc
						23	0.35 cc
						24	0.40 cc
						25	0.45 cc
						26	0.50 cc
						Gradually increase intervals	
						to monthly maintenance	
						Please read text to left	

NOTE: RECORD ALL INJECTIONS IN THE TREATMENT RECORD

NOTE: This dosage chart is offered as a recommended schedule.
However, the degree of sensitivity varies in many individuals. **IN THESE CASES THE SIZE OF THE DOSE AND INTERVALS BETWEEN DOSES MAY HAVE TO BE ADJUSTED AND SHOULD BE REGULATED BY THE PATIENT'S TOLERANCE AND REACTION.** Treatment is normally started with the weakest dilution in the set. Beginning with dose #1 as listed in the schedule. Doses should be administered at weekly or twice weekly

(at least 2 days apart) intervals while working up. The maintenance level is the largest dose tolerated by the patient that relieves symptoms without producing undesirable local or general reactions. *The intervals between maintenance doses can be increased gradually from 1 week to 2 weeks, to 3 weeks, to 4 weeks as tolerated. Then the maintenance can be given monthly.*

Use a 1cc tuberculin syringe with a 26-27 guage needle. Give injections subcutaneously to the posterolateral surface of the middle of the upper arm, staying away from the joints. Always pull back the plunger before injecting the extract. If blood returns, withdraw the needle and choose another site.

NOTE: PATIENTS ON BETA-BLOCKERS:
Recent evidence suggests that these patients may be more prone to anaphylaxis during immunotherapy and in such patients, anaphylaxis may be less responsive to conventional treatment. Hence in such patients, the need for continued immunotherapy and/or continued Beta-Blocker use should be carefully reviewed.

REORDER INFORMATION: To Reorder please call 519-745-9525 or Fax this Sheet to 519-745-9501

Reorder Date: _____

Lot Number Vial #1: _____

Lot Number Vial #2: _____

Special Requests: _____

Appendix: Sample Instructions

GENERAL INSTRUCTIONS FOR ALLERGEN IMMUNOTHERAPY INJECTIONS

CAUTION:

1. Health & Welfare Canada cautions that patients treated with beta-blocking agents might be more liable to react to allergenic drugs and that those reactions might not be controllable with epinephrine.
2. Refrigerate the allergen extract set. Do not freeze.
3. CHECK AND DOUBLE-CHECK ALL LABELS ON ALLERGEN BOTTLES BEFORE EACH INJECTION. HAVE THE PATIENT CONFIRM THAT THE EXTRACT BEARS THEIR NAME AND THAT YOU HAVE SELECTED THE CORRECT VIAL AND DOSE.
4. RECORD THE DATE OF THE INJECTION ON THE IMMUNOTHERAPY DOSAGE SCHEDULE, AND ALSO RECORD FULL DETAILS OF INJECTIONS ON THE "TREATMENT RECORD SHEET". DO INVOLVE THE PATIENT IN THIS – IT WILL MINIMIZE THE RISK OF A SERIOUS DOSAGE ERROR.
5. Check the expiry date on vial.
6. Shake the vial well before using it.
7. Make proper adjustments for late or missed doses:
 - A. If patient is receiving weekly or twice weekly injections:
 1. One week since the last dose, increase according to the schedule.
 2. Two weeks since the last dose, repeat the last dose.
 3. Three weeks since the last dose, reduce by two doses on the injection schedule then increase weekly according to schedule.
 4. Four weeks since the last dose, contact the prescribing physician.
 - B. If patient is receiving monthly maintenance injections:
 1. Four weeks or less since the last dose, repeat maintenance dose.
 2. For each week past four weeks, cut back one dose per week and then increase weekly according to schedule.
 3. Greater than eight weeks, contact the prescribing physician.
8. THE FIRST DOSE FROM A REFILL MAINTENANCE VIAL SHOULD BE 50% OF THE LAST DOSE GIVEN AND SHOULD THEN BE INCREASED WEEKLY ACCORDING TO SCHEDULE. New extracts are more potent than aged extracts.
9. Use a 1cc tuberculin syringe with a 26 – 27 gauge needle. Give injections subcutaneously to the posterolateral surface of the middle of the upper arm, staying away from the joints. Always pull back the plunger before injecting the extract: if blood returns, withdraw the needle and choose another site.
10. Do not massage the injection site and caution the patient not to do it either.
11. PATIENT MUST REMAIN IN THE OFFICE OR CLINIC FOR 30 MINUTES AFTER THE INJECTION, WITH A PHYSICIAN AVAILABLE.
12. BE AWARE OF HOW TO RECOGNIZE AND TREAT SYSTEMIC REACTIONS, AND OF HOW YOU MUST ADJUST DOSES FOR SIGNIFICANT LOCAL REACTIONS AND SYSTEMIC REACTIONS.
13. Patients should be warned not to eat a heavy meal just before an injection is to be given.
14. The patient should not participate in any strenuous physical exercise for several hours prior to and following the injection.
15. The safety of immunotherapy in pregnancy has not been established.
16. Patients should be ASSESSED ANNUALLY by a qualified consultant or more frequently if problems are encountered.
17. Clinical IMPROVEMENT in the allergy symptoms may be delayed for up to 2 years.
18. Consideration should be given to STOPPING INJECTION THERAPY after a period of several years.

PLEASE NOTE:

This schedule is enclosed as a guide to dosage and procedure. As always, the physician should exercise his or her own judgement based on his or her knowledge of the patient.

Note: New Vial Cutback- dose should be cut back to 1/2 of the previous month's dose. Rebuild the dose weekly as outlined in the dosage buildup schedule until the monthly maintenance dose is reached.

Left Arm

Right Arm

NOTE THE USE OF BETA BLOCKERS WITH THIS IMMUNOTHERAPY IS CONTRAINDICATED

