DOSE ADJUSTMENT SCHEDULES

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

Build-up phase for weekly or biweekly injections (time intervals from missed injection)

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

Dosage adjustment following time lapse between shots:

< 3 weeks between shots	proceed according to schedule
3-6 weeks between shots	repeat previous dose
7-12 weeks between shots	drop dose by 0.05ml for each week missed after 6th week
>12 weeks between shots	reevaluate patient

Table 1. Dose-Adjustment Schedule (Buildup and Maintenance Stages)

	Dose adjustments
For late injections, time since last injection, d (wk)	
≤14 (<2)	Increase volume per buildup schedule
15–28 (2–4)	Repeat volume of last dose
29–35 (4–5)	Decrease volume by 1 dose
36–42 (5–6)	Decrease volume by 2 doses
43–49 (6–7)	Decrease volume by 3 doses
50–56 (7–8)	Decrease volume by 4 doses
≥57 (>8)	Consult with allergist
For a new vial	Decrease volume by 50%
For a systemic reaction	Decrease by 1 vial (10-fold dilution)

BCH shot adjustment on the back of IT register – once maintenance reached
1 or 2 weeks: continue maintenance dose
3 weeks: reduce dose ½ of last dose
4 weeks: reduce dose to 1/3 of last dose
More than 4 weeks: call

Reaction Grades:

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects*

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. Portnoy method for numeric grading of reactions to allergen immunotherapy†

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Dosage adjustment for reactions

0-1+ **Proceed according to schedule**

2-3+ **Cut dose by one step. If tolerated, then advance again cautiously**

4-5+ **Give no more allergy shots until patient is re-evaluated. Consider 10 fold dilution.**

6+ **Give no more allergy shots until patient is re-evalauated. Give no futher injections from that vial.**

Effective doses

Extract	Labeled Potency	Optimal Dose (Volume added to 10cc assuming 0.5cc dose)	Final Amount in Extract
Cat (hair, pelt)	10,000 BAU/ml	3.5cc – 7.1cc	3500 – 7100 BAU
Timothy	100,000 BAU/ml	0.3cc - 1.1cc	3000 – 11,000 BAU
Ragweed	1:10	0.4cc - 0.7cc	1:145 - 1:250
D. pteryonissinus	10,000 AU/ml	0.4cc – 1.3cc	400 – 1300 AU
D. farinae	10,000 AU/ml	2.8cc – 6.1cc	2800 – 6100 AU
Mite mix	10,000 AU/ml	0.7 – 2.4 cc	700 – 2400 AU
Dog	1:10 (w/v)	5.0cc – 10cc	1:10 – 1:20
Other pollen	1:10	0.5cc – 1.0cc	1:100 – 1:200
Alternaria	1:10	1.0cc	1:100
Other molds	1:10	Unknown	1:100
Cockroach	1:10	Unknown	1:100
Bermuda	10,000 BAU	Unknown	Unknown

Doing the Math

- Concentration x volume = dose
- 10,000 BAU x 0.5ml = 5,000 BAU

- 1:100 (w/v) = 1gm/100ml = 10mg/ml

so

- 1:100 x 0.5ml = 5mg

Allergen	Concentration	Math	Dose
Cat Hair	10,000 BAU	10,000 BAU x 3ml/10ml	= 3000 BAU
Dog	10	1/10 x 1ml/10ml =	1:100
Grass Mix #4	10,000 BAU	10,000BAU x 2ml/10ml	= 2000 BAU
Mites mix	30,000 AU	15,000AU x .67ml/10ml	= 1000 AU
Tree Mix #9	1:110	1/110 x 5.5ml/10ml =	1:200
Plantain	1:10	1/10 x 1ml/ 10ml =	1:100
Ragweed	1:30	1/30 x 3ml/10ml =	1:100
Sagebrush	1:10		
AHAP	1:40	1/40 x 2.67 ml/10ml =	1:150
Cockroach	1:10		

Tree mix #9 = ash, white birch mix, boxelder/maple mix, cedar, cottonwood, elm Hickory, mulberry, oak
Grass Mix = Kentucky, bluegrass, orchard, red top, timothy

Cross-Reacting Families

1 Birch Family
- a) Birch
- b) Alder
- c) Hazelnut
- d) Hornbeam

2. Olive Family
- a) European olive
- b) Ash
- c) Russian olive

3 Fagaceae Family
- a) Oak
- b) Beech

4 Artemesia
- *a) Sages*
- *b) Wormwood*
- *c) Mugwort*

5 Ambrosia
- *a) Ragweeds*
- *b) Cocklebur*
- *c) Marshelder*

6 Chenopods
- *a) Russian Thistle*
- *b) Kochia*
- *c) Lambsquarters*

7 Amaranths
- *a) Pigweed*
- *b) Waterhemp*

8 Poplars Family
- a) Cottonwood
- b) Aspens
- c) Poplars

9 Juglandaceae Family
- a) Hickory
- b) Pecan

10 Northern pasture grasses
- a) Timothy
- b) June
- c) Orchard
- d) Meadow
- e) Fescue
- f) Redtop
- g) Sweet vernal
- h) rye

11 Bermuda

12 Johnson

13. Bahia

14. Cupressaceae Family
- a) Cedar
- b) Cyprus
- c) Juniper

HPI:
You are seeing patients on a busy August afternoon. You enter the exam room and find Karen Schotz, an 18 year old college student. She tells you that her allergies made her miserable during the last few months despite taking her medications and she wants to know if you think allergy shots would help.

Physical findings are consistent with nose and eye allergies: pale, edematous nasal mucosa, injected conjunctivae.

Skin testing is positive to: mouse, dust mites, trees, grass, weeds, mold, cat and dog

1. **What is immunotherapy?**
    i. Repeated administration of specific allergens to a patient with an *IgE-mediated* condition to provide protection against the inflammatory reactions associated with exposure.

2. **Indications for IT, what diseases can be treated:**
    i. Allergic rhinitis/conjunctivitis – poor response to medications, desire to avoid medication use or cost, medication side effects
    ii. Allergic asthma
    iii. Stinging insect hypersensitivity
    iv. Effective for pollen, fungi, animal dander, dust mite, cockroach, cat and dog.

3. **Not indicated for:**
    i. Atopic dermatitis
    ii. Food allergy
    iii. Chronic urticaria/angioedema

4. **Benefits/Risks: (consent form, patient handout, letter)**
    a. Benefits
        i. may not need medications, improved symptoms
    b. Risks
        i. include local and systemic reactions, we ask them to keep an epipen.

5. **Relative contraindications for AIT:**
    a. Severe psychological disorders
    b. Treatment with beta-blockers (including eye drops)
    c. Severe obstructive lung disease (limited reserve)
    d. Conditions that contraindicate epinephrine
    e. Unstable asthma (FEV1 < 70%)
    f. Severe coronary artery disease
    g. Inability to communicate clearly (?children < 5 years)
    h. Malignancy

6. **Describe the build up: At what concentration do you start? How often is it given? How long is the build up? What is maintenance?**
    i. Start at a 1,000 to 10,000 fold dilution
    ii. Dilute concentrations are more sensitive to degradation and lose potency more rapidly
    iii. Frequency of injections can vary: conventional vs. alternate schedules, we use 1x/week for 8-9 months
    iv. Maintenance dose is the final concentration – highest dose projected to be therapeutically effective
    v. The intervals for maintenance range up to 4 weeks for inhalant allergens and up to 6 weeks for venom allergens

7. **When would you expect to see clinical improvement? If no improvement?**
    i. Demonstrated after reaching the maintenance dose.
    ii. If no improvement is noted after 1 year of maintenance, reassess.
    iii. Patients should be seen in clinic every 6 to 12 months while receiving IT
    iv. Duration of maintenance is 3 to 5 years (individualized based on clinical response, disease severity, IT reaction hx, patient preference).

8. **What if the patient becomes pregnant?**
    a. Allergen IT is usually not initiated in pregnant patients
    b. Dosing should NOT be advanced during pregnancy
    c. Immunotherapy may be continued if the benefit outweighs the risk – life threatening venom allergy
    d. Patients should be counseled regarding potential for severe systemic reactions compromising the health of the unborn baby
    e. If pregnancy occurs and the patient is getting a dose unlikely to be therapeutic, discontinuation of IT should be considered.

9. **Back to our original patient (computer)**
    a. Write an IT rx – what should be included
        i. the maintenance concentrate should be prepared and labeled for each patient (picture)
    b. What can be combined
        i. High protease activity
            1. Mold
            2. Cockroach
        ii. Low protease activity
            1. Grass pollen, Tree pollen, Weed pollen (except ragweed), Animals (cat and dog)
        iii. Other allergens
            1. Ragweed can be mixed with either group
            2. Insect venoms require separate vial and injection

c. Optimal concentrations

10. **Extracts**:
    a. Standardized extracts
        i. Cat hair, cat pelt, DP, DF, short ragweed, Bermuda grass, Kentucky, rye, orchard, timothy, fescue, red top, vernal, hymenoptera venoms (yellow jacket, honeybee, wasp, yellow hornet, and white faced hornet).
    b. Non–standardized: Fungal extracts

11. Suggestions to reduce the risk of reactions to allergy shots
    a. Can start at a very dilute concentration
    b. Antihistamine
    c. Reduce dose

12. What are the types of build up protocols
    a. Traditonal
    b. Cluster
    c. Rush

13. When do you make dose adjustments
    a. Local reactions
        i. treatment – cold compress, topical corticosteroids, antihistamines.
        ii. paper from annals
    b. Missed doses – anecdotal experience
    c. New vials

14. What are risk factors for systemic reactions
    a. Errors in dosing
    b. Symptomatic asthma
    c. A high degree of allergen hypersensitivity
    d. Concomintant use of Beta blocker
    e. Injections from new vial (0.25ml, 0.4ml, 0.5ml)
    f. Injections during allergy season and pt is symptomatic

15. How do you evaluate effectiveness of IT
    a. reduced symptoms during seasons of allergen exposure
    b. reduced medication requirements
    c. improved objective findings on exam