Immunotherapy Safety for the Primary Care Provider

To begin, click the Bookmark Tab or Icon to the left to open the *Table of Contents*. Click on the + next to a topic to reveal the available slideshow & reference articles. Open your selection by moving the cursor over the title and left click once.

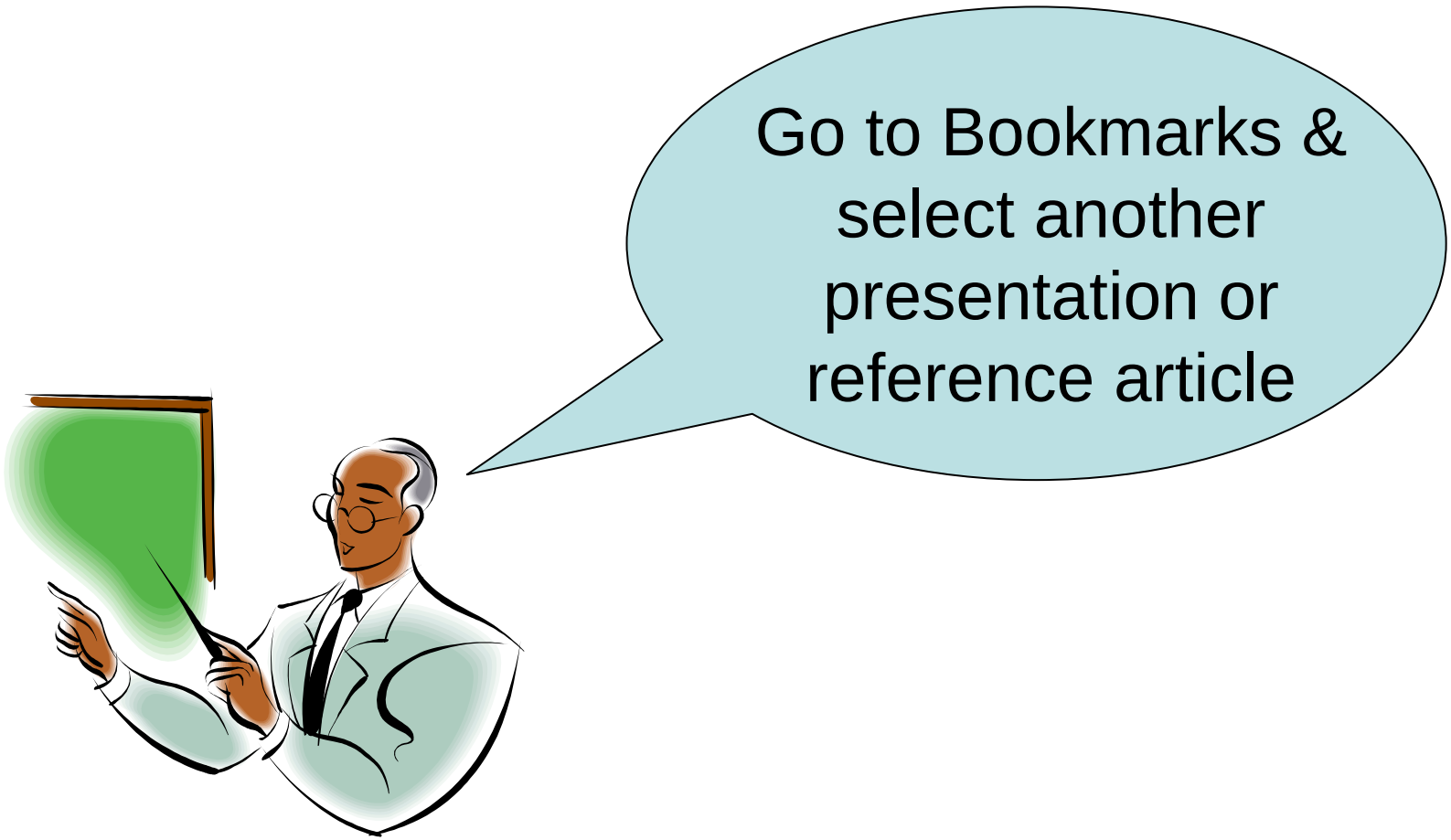
Left click with the cursor positioned over the first page/slide, then use the Page Up/Down keys to proceed through the presentation. When an item is complete, an “end of selection” page will appear.

I hope you find this material useful & the CD format convenient.

Capt. J. Montgomery MC, USN

February 04, 2008

End of Selection



Welcome to
"Immunotherapy Safety for the Primary Care Provider" or "Optimizing the Safety of Immunotherapy Administration Outside of the Allergist's Office"

I am deeply indebted to the American Academy of Allergy, Asthma, and Immunology's Immunotherapy & Allergy Diagnostics Committee and to the Immunization and Allergy Specialty Course of the Walter Reed Army Medical Center for much of the material contained within this training CD.

The purpose of this CD is to provide a comprehensive overview of allergen immunotherapy for primary care physicians and their ancillary staff with a primary focus on risk factors that affect immunotherapy safety and measures that may enhance immunotherapy safety.

Learning Objectives:

1. Understand immunotherapy indications, potential risks, contraindications, protocols, potential mechanisms and risk factors for systemic reactions after allergen and vaccination injections.
2. Be familiar with the current recommended guidelines in terms of proper personnel and emergency equipment required for administration of allergen immunotherapy and adult and pediatric vaccines.
3. Recognize the signs and symptoms of adverse immunotherapy reactions and the appropriate treatment for them.
4. Apply the greater understanding of potential risks associated with immunotherapy and immunizations into a clinical practice with office protocols designed to screen high risk individuals prior to receiving injections and to make appropriate clinical decisions based on this screen.
5. Apply the competencies and learning assessments contained herein to assure the safe administration of immunotherapy and vaccines.

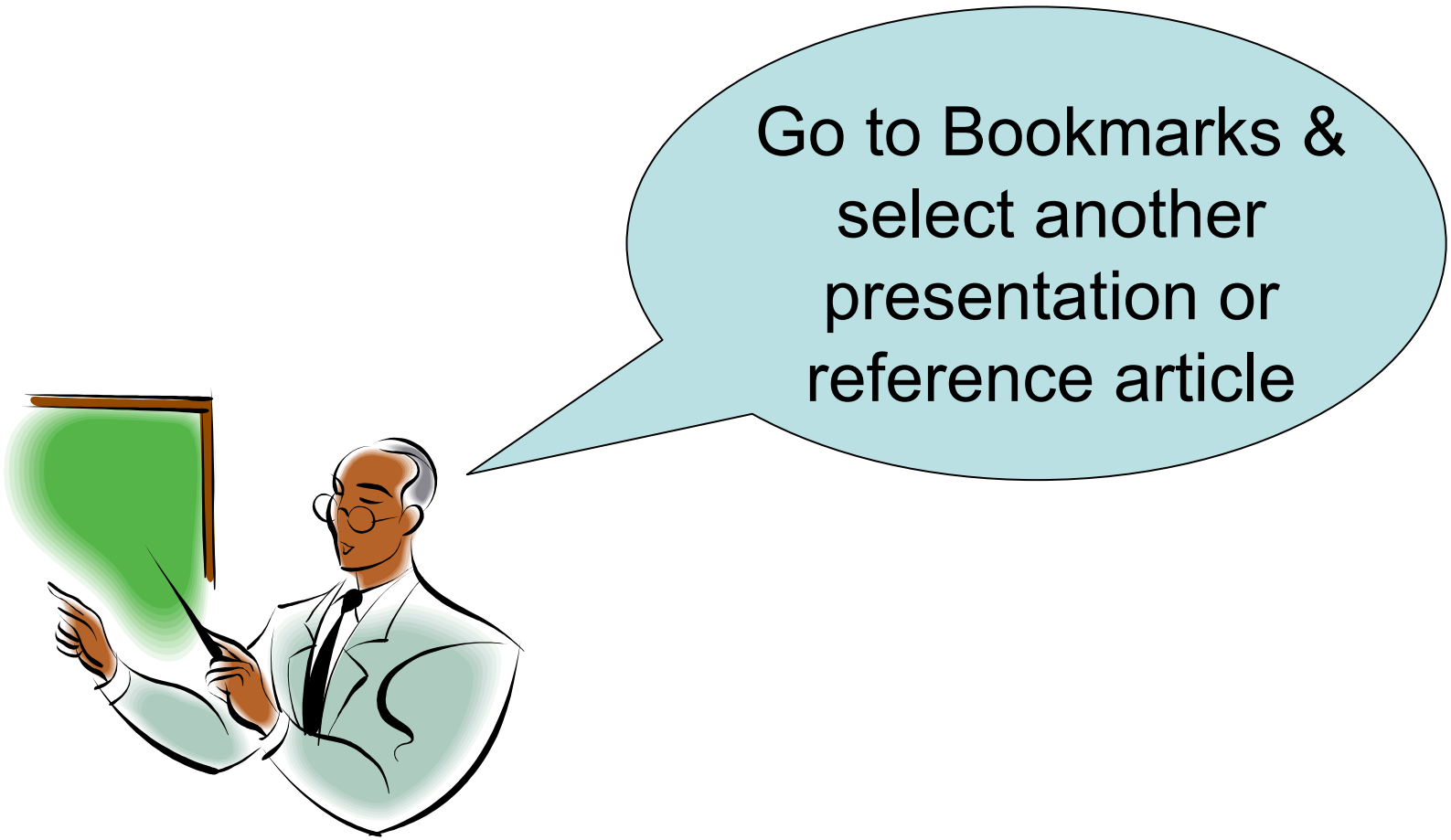
CD format: The didactic program begins with the lecture slide show. Handouts include a lecture summary and a position statement addressing administration of allergen immunotherapy by non-physician staff, as well as suggested formats for a clinic SOP, nurse/technician competency assessment, patient informed consent, AIT administration form, and a dosage adjustment guide. Upon completion of this program, participants are encouraged to take the included self-assessment test.

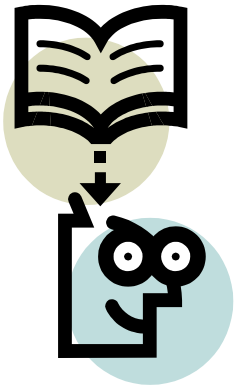
I hope that you find the material helpful and the format convenient.

Capt. Jay Montgomery MC, USN
Head, Division of Allergy & Immunology
National Naval Medical Center

Production Team: Ms. Sally Bentsi-Enchill, HM3 Harrison Wright USN, Ms. Anna Harrison, Ms. Denise Chambers, and HN Joy Lewis USN

End of Selection





Click the ☒ next to the topic to view the slide show & reference articles

Immunotherapy for the Primary Care Provider

-or-

Optimizing The Safety Of Immunotherapy Administration Outside Of The Prescribing Allergist's Office

Jay Montgomery MD, FAAFP, FAAAAI
Captain, Medical Corps, United States Navy
Head, Division of Allergy & Immunology
National Naval Medical Center

Immunotherapy at Remote Sites
Standard of Care

- In the case of professionals, the standard of care refers to the level of care that a reasonable professional in the same or similar circumstances would take to prevent harm or injury to another person.
- "The standard of care concerning the administration of immunotherapy should be the same regardless of where the immunotherapy is given and the specialty of the supervising physician."

Position Statement on administration of immunotherapy outside of the prescribing allergist facility. Drug and Anaphylaxis Committee of ACAAI. Ann Allergy Asthma and Immunol 1998;81:101-102

What is Immunotherapy?

- Gradually increasing quantities of specific allergens to an optimal dose
- Raises the patient's tolerance to the allergens
- Thereby minimizing the symptomatic expression of the allergic disease
- Allergen extract vs Allergen vaccine
  - Proteins 'extracted' from various materials
  - 'Immune modifier'

What Immunotherapy Is Not

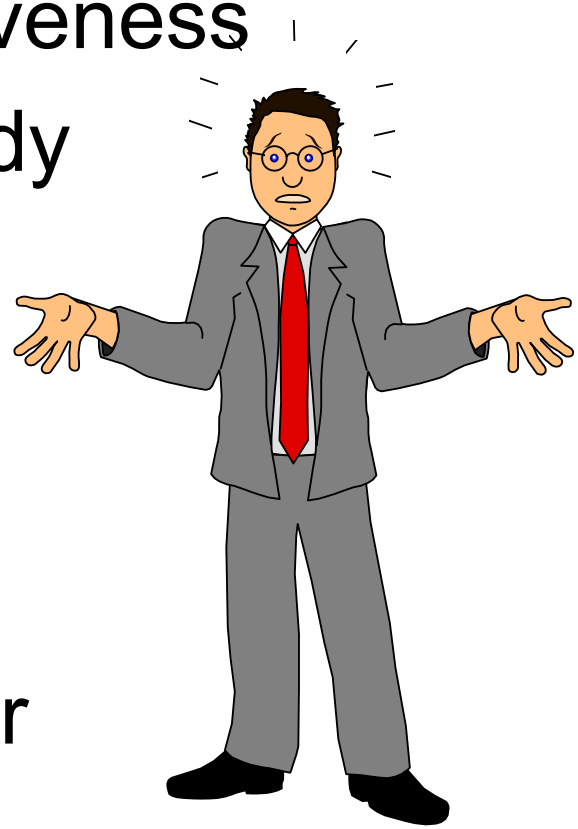
- Not prescribed by a remote laboratory:
  - Immunotherapy should be prescribed by physicians specifically trained to diagnosis and treat allergic diseases.
- Not based on skin test or in vitro tests alone:
  - Treatment MUST be based on the combination of a thorough history and physical exam and allergy tests.
- Not administered at home
  - Must be administered in a properly equipped facility staffed with personal able to recognize/ treat IT systemic reactions.

What Immunotherapy Is Not

- Not administered through non-injectable routes
  - Subcutaneous route is the only approved method in the U.S.; sublingual route currently is not approved by FDA.
  - Sublingual immunotherapy used outside of US, but with higher doses (10- 500 x subcutaneous IT) may make treatment cost prohibitive. Further studies required before approved in US.

How Does Immunotherapy Work?

- Decrease in cellular responsiveness
- Production of blocking antibody
- Induction of tolerance (B-cell, T-cell, or both)
- Presence of anti-idiotypic antibodies
- Activation of T-cell suppressor mechanism



History of Immunotherapy

1911

- Leonard Noon at the St. Mary's Hospital, London injected extract of grass pollen into a patient whose symptoms coincided with the pollinating season of grasses

1965-present

- Norman, Lichtenstein, et. al. defined AIT effectiveness in allergic rhinitis, allergic conjunctivitis, allergic asthma, and hymenoptera hypersensitivity

Who Benefits?

- Those with…
  - Allergic disease identified through an adequate history & in vivo testing (in vitro testing is not adequately specific)
  - Well-defined clinically relevant allergic triggers
  - Significant effect on quality of life or daily function
  - Inadequate relief through avoidance measures and pharmacotherapy

What Benefits?

- Marked reduction in allergy symptom scores
- Marked reduction in medication use
- Reduced sensitivity to other allergens
- May prevent progression or development of multiple allergies
- May reduce risk of later development of asthma

Immunotherapy Efficacy

- Effective treatment for allergic rhinitis
  - A meta-analysis of 18 studies involving 789 patients concluded that AIT is effective in the treatment of allergic rhinitis.[1]
- Effective treatment for asthma
  - Two meta-analyses of 43 prospective studies showed that AIT is effective in the treatment of allergic asthma.[2,3,4]
- Highly effective treatment for insect venom allergy
  - A meta-analysis of 9 studies indicated that a course of venom immunotherapy (VIT) is highly effective in the management of insect sting hypersensitivity.[5,6]

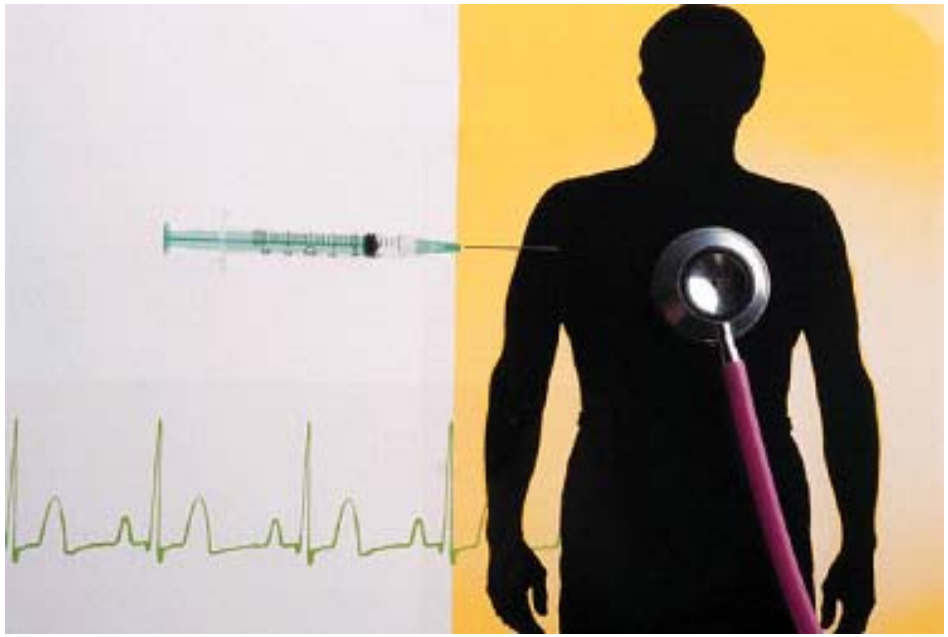
Indications for Immunotherapy

- Hymenoptera venom hypersensitivity, allergic rhinitis, allergic conjunctivitis, and allergic asthma
- Desire to avoid long-term use or potential adverse effects of medications
- Symptoms not adequately controlled by avoidance and pharmacotherapy
- Cost of immunotherapy is less than cost of long-term medications

Not Efficacious For…

- Atopic dermatitis
- Urticaria
- Headaches
- Food allergies

Allergen Immunotherapy



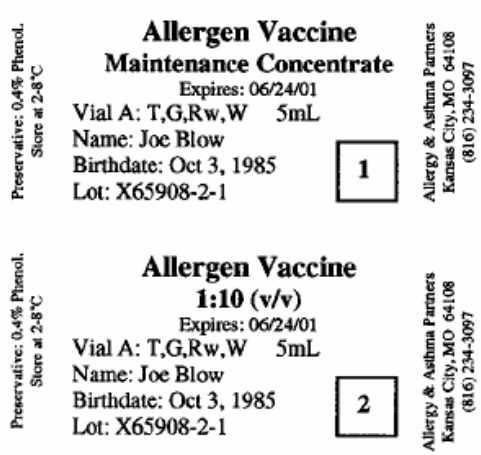
Safety

The Extracts/Vaccines

- Bioequivalent Allergy Unit (BAU)
  - Determined through quantitative skin testing on a reference population of allergic patients highly skin-test reactive to that allergen
- Standardized Allergens
  - Cat, Bermuda & Northern Pasture Grasses (3), Dust Mite (2), and Ragweed
- Non-standardized Allergens
  - Wt/V or PNU

The Extracts

- Storage
  - Refrigerated at 4°C (39°F)
    - Loss of potency within weeks at room temp
    - More concentrated = more stable
- Identification
  - Name & identifying number (SSN, DOB, etc.)
  - Contents of vial
    - Tree: T, Mold: M, Grass: G, Cat: C, Weed: W, Dog: D, Ragweed: R, Cockroach: Cr, Dust Mite: Dm
  - Expiration date
  - Dilution v/v (from maintenance vial)
  - Number identifier (#1=maintenance=red cap)
  - Standard colored caps
    - Red= 1:1, yellow= 1:10, blue= 1:100, green= 1:1,000

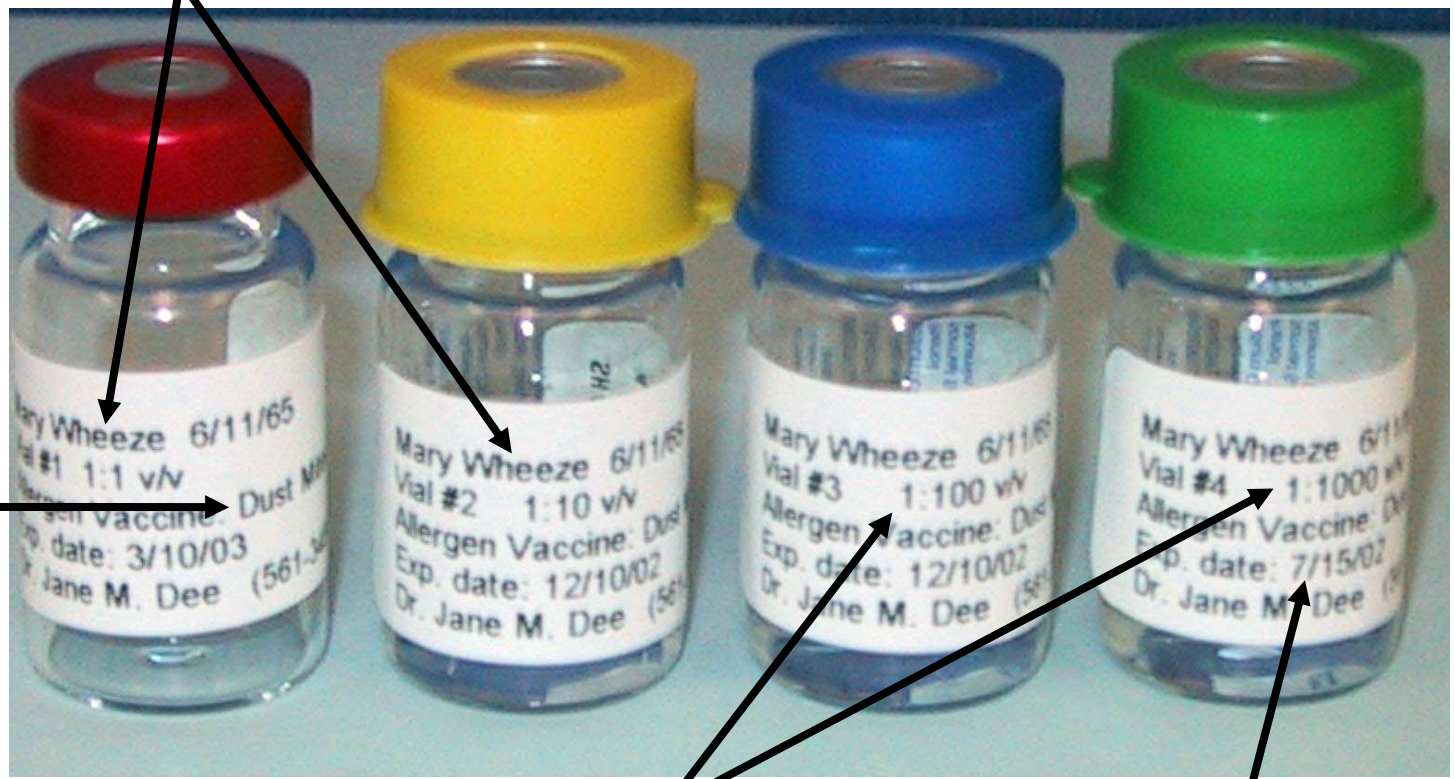


Lots of Numbers!

Vial	v/v	W/V (example)	AU/ML (example)	BAU/ML (example)
1 Red	1:1 (maintenance)	1:100	2000	7750
2 Gold	1:10	1:1,000	200	775
3 Blue	1:100	1:10,000	20	77.5
4 Green	1:1000	1:100,000	2	7.75
5 Silver	1:10,000	1:1,000,000	0.2	.775

Dilution Labeling, Color-Coding and Vial Nomenclature

Patient's name on all vials

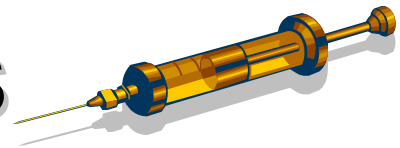


Contents

Vial concentration

Expiration date

Immunotherapy Phases

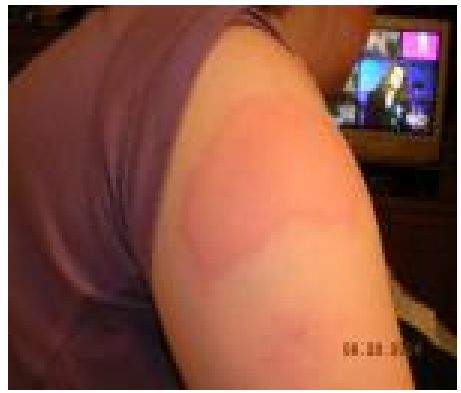


- Maintenance concentration = therapeutically effective dose as determined by the Allergist
- **Build up phase** (vials up to & including maintenance vial)
  - Involves receiving injections of increasing amounts of allergen(s)
  - Frequency of injections ranges from 1 - 2 times a week, although more rapid build-up schedules are possible.
  - The duration of this phase generally ranges from 3 to 6 months, depending upon the frequency of the 18-27 injections.
- **Maintenance phase** (maintenance vial)
  - Begins when the effective therapeutic dose is reached.
  - Differs for each person, depending on their level of allergen sensitivity (how 'allergic' they are to the allergens in their vaccine) and their response to the build-up phase.
  - The intervals between maintenance immunotherapy injections generally ranges from 2 to 4 weeks (3-4 weeks).
  - Administered for 3-5 years.
- **AIT schedules ≠ VIT schedules**

Immunotherapy Reactions

Local reactions:

- Are fairly common
- Present as redness and swelling at the injection site.
- Can happen immediately, or several hours after injections.



Systemic reactions:

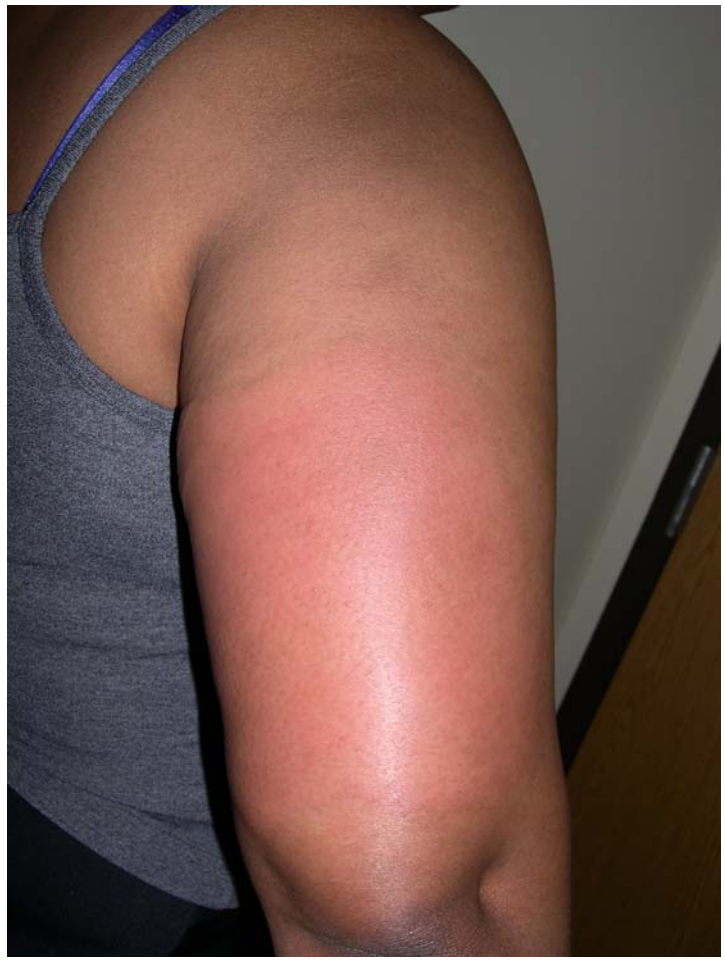
- Less common
- Include allergy symptoms such as sneezing, itching palms, nasal congestion, or hives.
- Can include swelling in the throat, wheezing or a sensation of tightness in the chest, nausea, dizziness, fainting, and/or other severe systemic symptoms.
- Systemic reactions require immediate treatment.

Reaction Prevention - Avoidance

- Circumstances warranting dose change
  - *Follow prescribing Allergist's written instructions*
  - Missed doses
    - Buildup phase
    - Maintenance phase
  - Reactions, local or systemic
    - Local >1" (quarter size) or lasts >12 hr
    - Systemic
  - Renewed maintenance vial - reduce dose 50%
  - Communication with Allergist ALWAYS!

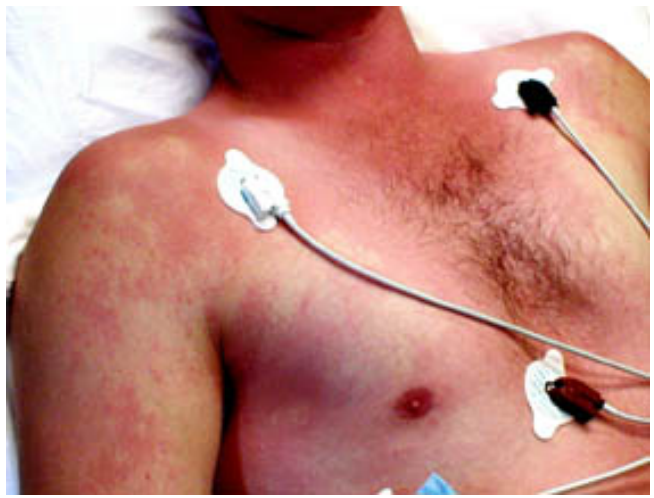
Reaction Therapy – BLS+ Level

- Treatment of local reactions
  - Local reaction
    - Cold pack, oral antihistamine, topical steroid
  - Large local reaction (Arthus reaction)
    - Oral steroids, NSAIDs, oral antihistamines



Reaction Therapy – BLS+ Level

- Treatment of systemic reactions
  - Anaphylaxis 3%, Death 1:1,000,000
- Training and Equipment for Basic Life Support
- Physician at bedside w/in 2-3 minutes
- ABC assessment TO BE PERFORMED AT THE SAME TIME AS THE ADMINISTRATION OF **EPINEPHRINE**



Treatment Guidelines

- Treatment (airway/breathing)
  - Maintain an open airway
  - High flow oxygen (4-10 l/m) with pulse oximetry
  - Intubation when $PaCO_2$ >65 mm Hg / SaO_2<90% on O_2
- Treatment (circulation)
  - Keep Systolic BP > 90 mm Hg
  - Place patient in Trendelenburg position
  - Insertion of large-bore IV
    - 0.9% saline
  - Severe Hypotension
    - Dextran, Hetastarch

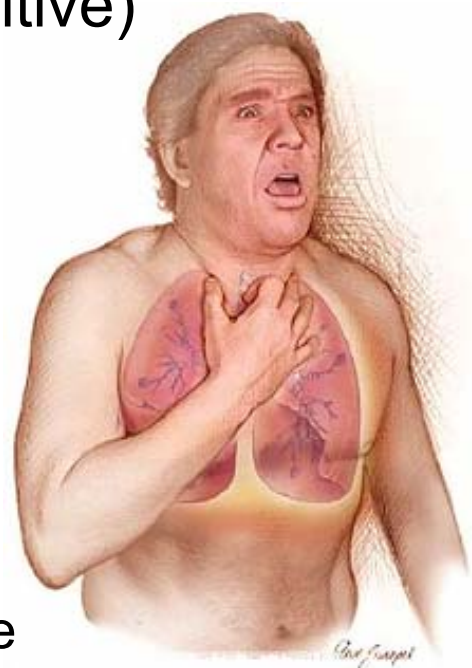
Treatment Guidelines

- Treatment (drugs)
  - EPINEPHRINE
    - 0.3 - 0.5 cc 1:1,000 IM adult
    - 0.01cc/kg 1:1,000 IM child
    - Repeat q 10 min prn
    - Glucagon 1-5 mg over 2-5 min IV push

  - Antihistamines
    - Diphenhydramine (Benadryl): 50-75 mg IM/IV adult
      1-2mg/kg IM/IV child
    - Cimetidine (Zantac): 300 mg q6-8 hr PO/IV
  - For Bronchospasm - Albuterol MDI/Nebulized
  - Methylprednisolone 60 - 80 mg IV

Immunotherapy Contraindications

- Who?
  - Conditions posing reaction survivability risk
    - Lung disease with FEV_1 <50% predicted
    - Poorly controlled asthma (PF <70% predicted)
    - B-blocker use (relative, venom sensitive)
    - Failure of a major organ system
    - Unstable angina
    - Uncontrolled hypertension
  - Unable to report problem
  - Non-compliant patients
  - Pregnant patients (relative)
    - Don't initiate; may continue on maintenance



Frequency of Systemic Reactions

- 0.8% to 46.7% (mean 12.92%) systemic reaction rate for conventional AIT schedule.

  Stewart GE and Lockey RF *J Allergy Clin Immunol* 1992; 90: 567-78

- 45% of reactions occur in patients who have had previous systemic reactions.

  Matloff SM *et al Allergy Proceed* 1993; 14: 347-350

Worse Case Scenario: Fatalities

- 46 fatalities between 1945 and 1984
  - 10 fatalities during seasonal exacerbation
  - 4 fatalities in patients symptomatic prior to injection
  - 22/30 onset of reaction within 30 minutes

    Lockey RF, et. al., *J Allergy Clin Immunol* 1987; 79: 660-77
- 17 fatalities between 1985 and 1989
  - 76% had asthma, 36% reported prior systemic reactions
  - 5 – new vial, 5 – dosing error, 4 – prior symptoms
  - 11/17 onset anaphylaxis within 20 minutes

    Reid MJ, et. Al., *J Allergy Clin Immunol* 1993; 92: 6-15
- 41 fatalities between 1990 and 2001
  - **Death rate of 1 per 2,540,000 injections**, 3.4 deaths per year
  - 15 were asthmatic not optimally controlled
  - 3 deaths in patients receiving AIT **outside** of a medical facility
  - Most occurred with maintenance concentrates

    Bernstein DI, et al., *J Allergy Clin Immunol* 2004; 113: 1129-36

Immunotherapy Safety

- To lessen risk of reaction
  - Identify patient (100%)
  - Check health status
    - Acutely ill, asthma/allergy exacerbation, new medications?
    - Previous delayed reactions?
  - Use standard immunotherapy administration form
    - **R**ight Patient (check ID)
    - **R**ight Extract (extract contents / Rx number must be on vial)
    - **R**ight Strength (extract cap color, written concentration)
    - **R**ight Time (date of injection is within prescribed schedule)
    - **R**ight Dose (have patient verify vial # and amount drawn)
  - Document everything!

Immunotherapy Safety

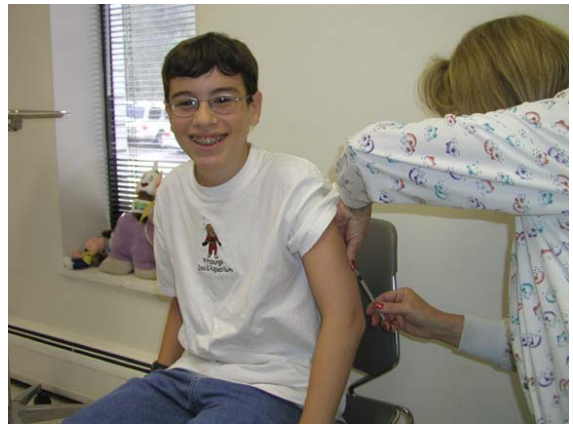
- To lessen risk of reaction
  - Allergen immunotherapy should be given in settings where emergency resuscitative equipment and trained personnel are immediately available to treat systemic reactions under the supervision of a physician or licensed physician extender."
  - Patients at high risk for systemic reactions (those who are highly sensitive or have severe symptoms, co-morbid conditions, or a history of recurrent reactions) should receive immunotherapy in the office of the Allergist. The Allergist who prepared the patient's vaccine and the support staff should have experience and procedures in place for administering immunotherapy to high-risk patients.

- Position Statement On: Administration Of Immunotherapy Outside Of The Prescribing Allergist Facility. Ann Allergy Asthma and Immunol 1998;81:101-102
- Allergen Immunotherapy: a practice parameter. Ann Allergy Asthma and Immunol 2003;90:1-40

Immunotherapy Safety

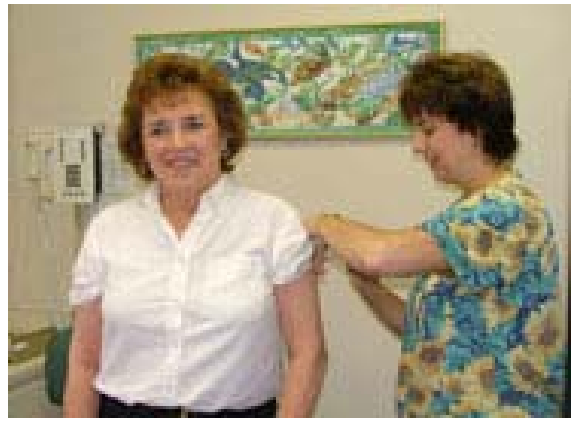
- To lessen risk of reaction
  - Trained personnel should be familiar with the following procedures:
    - Adjustment of dose of allergen immunotherapy extract to minimize reactions.
    - Recognition and treatment of local and systemic reactions to immunotherapy injections.
    - Basic cardiopulmonary resuscitation.
    - Ongoing patient education in recognition and treatment of local and systemic reactions that occur outside the Allergist's office.”

Immunotherapy Safety



- Injection
  - Once patient and extract verified …
    - Wipe injection site (the dorsal aspect of upper arm, halfway between elbow and shoulder).
    - Wipe extract tops with alcohol, draw up extracts per protocol.
    - With gloved hands, administer injections subcutaneously at a 90° angle with 1/2 - 5/8 inch needle or 45° angle with 1 inch needle after first drawing back plunger & checking for blood.
    - Hold 2x2 on site firmly for a few seconds. Do not rub.
    - Dispose of syringe and needle in the sharps container.
    - *NEVER RE-CAP NEEDLES.*
    - Apply band aid/ice/ topical steroid cream, if needed.

Immunotherapy Safety



- After Injection
  - After 30 minutes, examine the injection sites for induration and/or erythema.
  - Document all findings on the AIT shot record.
  - Document any protocol-directed dose reductions of future injections on the AIT shot record and SF-600.
  - If needed, further modify dose reduction instructions as per delayed reaction dose-reduction protocol.

Immunotherapy Safety

- Patient instructions:
  - Must remain in clinic 30 minutes after injection.
  - Have staff inspect site(s) for swelling before leaving.
  - Report any abnormal signs or symptoms to staff immediately.
  - Don’t exercise for 2 hrs after receiving AIT.
  - Notify staff prior to next shot of any delayed reaction.
  - Keep to their AIT/VIT schedule.

Immunotherapy Safety

- Equipment:
  - Aeroallergen & venom extract storage (4º C refrigerator with alarm)
  - 1 ml (for AIT) & 3ml (for VIT) disposable (safety) syringes with 27gauge 5/8 inch needles
  - Epi-pen Auto-injectors 0.3mg for adults & 0.15mg for children
  - Alcohol pads
  - 2x2 gauze pads
  - Gloves
  - Sharps container
  - Crash cart – BLS+ level
    - Vital signs monitor, SO_2
    - Equipment to establish an oral airway
    - AMBU bag & oxygen equipment
    - Intravenous access/fluids
    - Injectable epinephrine
    - Injectable antihistamine
    - Injectable steroids
  - Phone (911)

So You Still Want to Give Shots?

- What is needed?
  - Good communication between you and your Allergist
    - Precise instructions/protocols IAW ACAAI Practice Parameters
    - AIT/VIT Vials labeled IAW ACAAI Practice Parameters
    - Precise descriptions of reactions and their treatment
  - Facility
    - Refrigeration, supplies
    - Standard forms
    - Equipment to manage anaphylaxis (ABCD's)
  - Personnel
    - Trained to give shots, recognize and treat anaphylaxis
    - Staff BLS capable
    - Physician available within 2-3 minutes

What To Expect (Demand) from the Allergist

- A record of previous responses to and compliance with the allergy shot program
- Full, clear, and detailed documentation of the patient's immunotherapy schedule
- General instructions for administration of immunotherapy
- Recommendations for dose adjustment for reactions & unexpected intervals between shots
- Instructions on how to treat reactions to immunotherapy injections

Li JT, et. al., Allergen immunotherapy: A Practice Parameter. *Ann Allergy Asthma Immunol* 2003; 90(suppl).

Summary

- Immunotherapy is an effective and potentially disease-modifying treatment for asthma, allergic rhinitis and stinging insect anaphylaxis.
- Effectiveness of immunotherapy depends on appropriate dose and duration of treatment.
- Serious reactions to immunotherapy are uncommon.
- Appropriate safety measures based on known risk factors may prevent or reduce incidence of serious reactions.

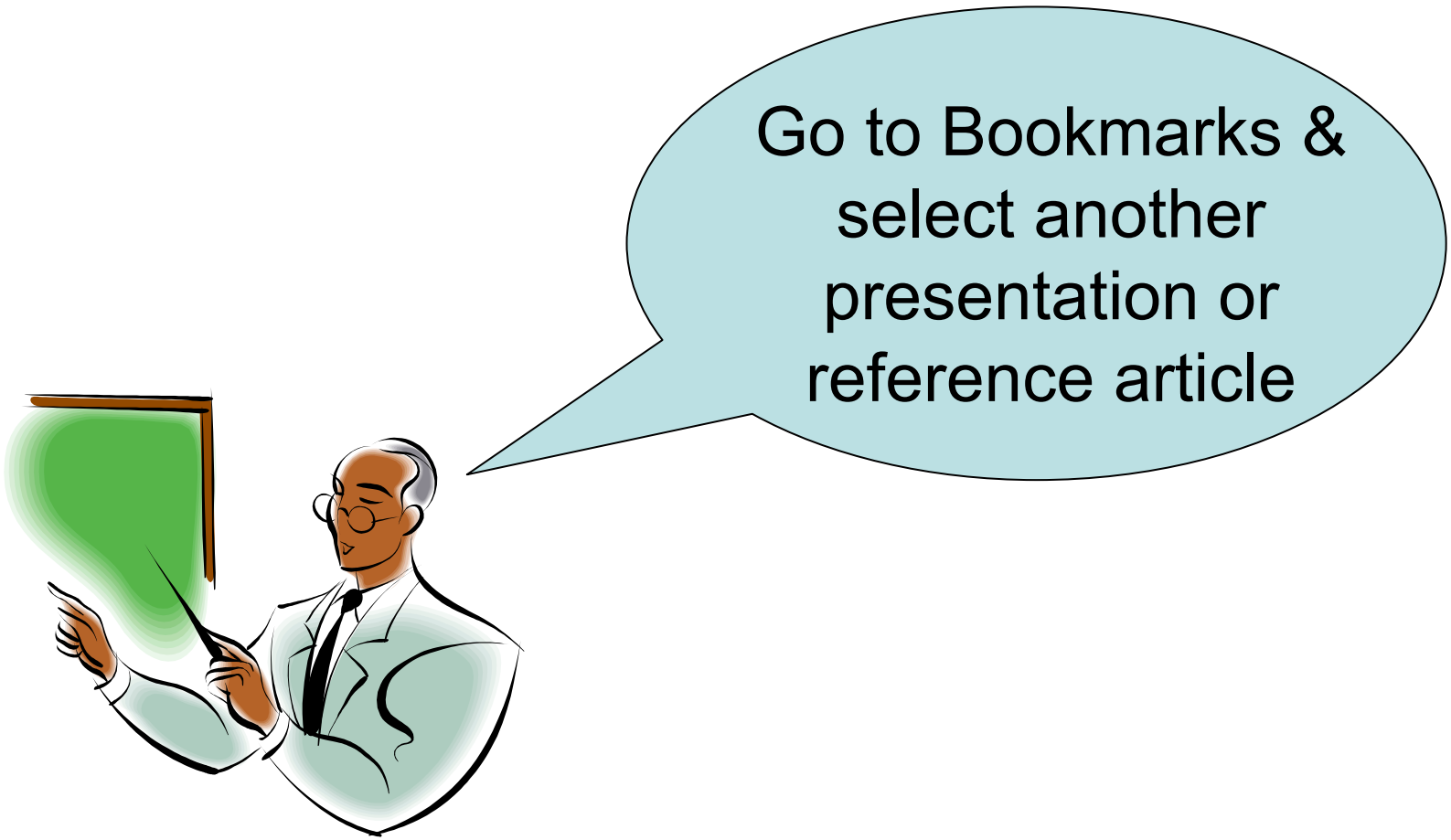
Summary

- Risk factors for adverse events during immuno-therapy administration include:
  - "A Momentary Lapse in Concentration"
    - Check and double-check
      - **R**ight Patient (check ID)
      - **R**ight Extract (extract contents / Rx number must be on vial)
      - **R**ight Strength (extract cap color, written concentration)
      - **R**ight Time (date of injection is within prescribed schedule)
      - **R**ight Dose (have patient verify vial # and amount drawn)
  - Presence of symptomatic asthma
    - Do not administer allergy shot(s) until asthma is stable and PF > 70% of personal best.

Summary

- Risk factors for adverse events during immuno-therapy administration include:
  - Use of beta-blockers: ask about ALL new medications each visit
  - Injections from new vials: dosage adjustment per prescribing allergist – review previous schedules
  - High degree of shot sensitivity
    - Consider premedication
    - Consult prescribing allergist if recurrent and/or persistent large local reactions
    - Always consult allergist before further administration if patient experienced a systemic reaction with the previous injection

End of Selection



ALLERGY IMMUNOTHERAPY

For the Nurse/Technician

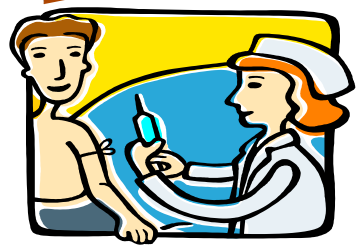
EQUIPMENT

- Alcohol pads
- 2x2 gauze pads
- 1ml for (AIT) & 3ml for VIT disposable (safety) syringe with 27gauge 5/8’ needle
- Aeroallergen or venom extract
- Epinephrine autoinjector 0.3mg for adults and 0.15mg for children

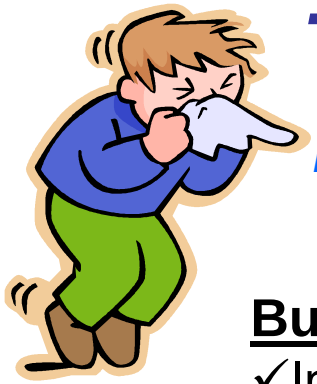
- Glucagon
- Vital Signs monitor
- Oxygen administration equipment
- Crash cart
- Gloves
- Tourniquet
- Sharps container


Safety needles

What is immunotherapy?



- Allergen immunotherapy (allergy shot) is a form of treatment aimed at decreasing sensitivity to substances called allergens.
- Allergens are the substances that trigger your allergy symptoms when you are exposed to them and are identified by allergy testing.
- Allergen immunotherapy involves injecting increasing amounts of an allergen until a maintenance dose is reached and continued over 3 to 5 years.
- Immunotherapy has been shown to decrease current symptoms, prevent the development of new allergies and, in some children, prevent the progression of the allergic rhinitis to asthma.
- Allergen immunotherapy can result in long-lasting relief of allergy symptoms after treatment is stopped.



The 2 Phases of Immunotherapy

Prior to immunotherapy; provide patient with immunotherapy education packet and review material with patient to his/her/guardian's full understanding and satisfaction.

Build-up phase:

✓Involves receiving injections with increasing amounts of allergens.

✓Frequency of injections during this phase generally ranges from 1 to 2 times a week, though more rapid build-up schedules are sometimes used.

✓The duration of this phase depends on the frequency of the injections but generally ranges from 3 to 6 months.

Maintenance phase:

✓This phase begins when the effective therapeutic dose is reached.

✓The effective maintenance dose is different for each person, depending on their level of allergen sensitivity (how 'allergic they are' to the allergens in their vaccine) and their response to the immunotherapy build-up phase.

✓Once maintenance dose is reached, there will be longer periods of time between immunotherapy shots. The intervals between maintenance immunotherapy injections generally ranges from every 2 to every 4 weeks.

BEFORE EACH SHOT!!!

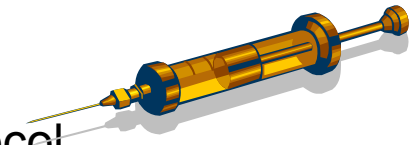
- Screen patient's current health and medication status.
- Perform these safety checks:
  - **R**ight Patient (positively confirm – photo ID, etc.)
  - **R**ight Extract (extract contents, prescription #, & name must be on vial)
  - **R**ight Strength / Color/ Concentration
  - **R**ight Time (make sure date of injection is within prescribed schedule)
  - **R**ight Dose (have patient verify vial # and amount drawn correct)

  * **P**atient verification of all the above.

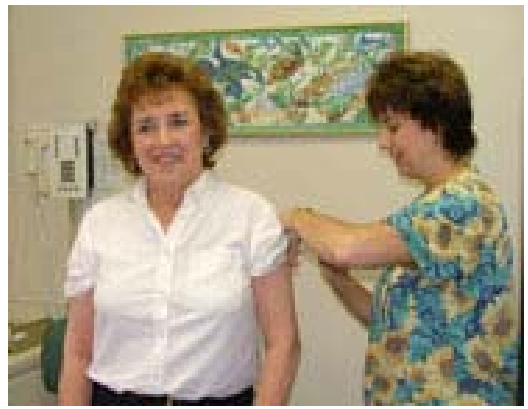
- **All asthmatic patients receiving immunotherapy must perform peak flow measurements (three measurement attempts) with best reading meeting or exceeding set parameters, prior to injections!**

procedure

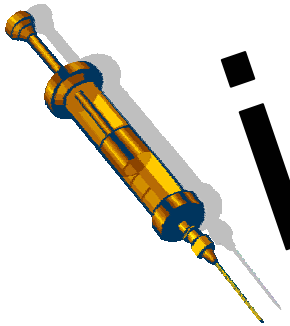
- ✓ Wipe injection site (the dorsal aspect of upper arm, halfway between elbow and shoulder).
- ✓ Wipe tops of extracts with alcohol, draw up extracts per protocol.



- ✓ With gloved hands, administer injections **<u>subcutaneously</u>** at a 90^0 angle with ½ - 5/8 inch needles or 45^0 angle with 1 inch needle.
- ✓ Hold 2x2 on site firmly for a few seconds. <u>Do not rub</u>.
- ✓ Dispose of syringe and needle in the sharps container
- ✓ ***<u>NEVER</u> RE-CAP NEEDLES.***
- ✓ Apply band aid/ice/ topical steroid cream, if needed.

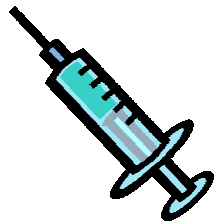


- ✓ Instruct patient to <u>remain in the waiting area for 30 minutes</u> after the allergy injection and return to the treatment (injection) room to have area checked and documented prior to leaving the clinic.

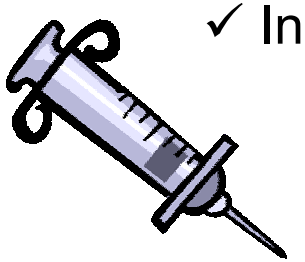


instructions!

- ✓ instruct patient to report any abnormal signs and or symptoms they may experience to staff immediately for appropriate medical intervention.
- ✓ After 30 minutes, feel the injection sites for any swelling (induration); also note any redness (erythema).
- ✓ Document any initial findings on AIT record per reactions instructions noted below.



- ✓ Document further dose reduction instructions for future injections per physician's orders on the SF-600 and on the treatment record, based on reactions.

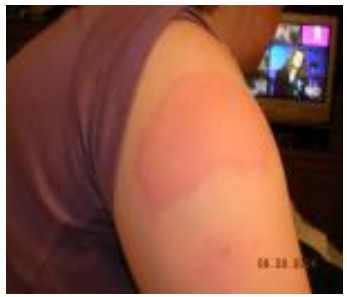


- ✓ Instruct patient to notify staff of any delayed reactions after they leave the clinic, prior to injections. Follow "Grading" delayed reactions dose reduction protocol below for injections.

2 Types of Reactions

Local reactions:

- Are fairly common
- Present as redness and swelling at the injection site.
- Can happen immediately, or several hours after injections.



Systemic reactions:

• Less common.
• Include increased allergy symptoms such as sneezing, nasal congestion or hives.
• Can include swelling in the throat, wheezing or a sensation of tightness in the chest, nausea, dizziness, fainting, and/or other severe systemic symptoms.
• Systemic reactions require immediate treatment. See treatment for anaphylaxis.

GRADING REACTIONS & ADJUSTING DOSE

- **Negative** (swelling up to 15mm; i.e., dime size) – progress according to schedule.

- **"A"** (swelling 15-20 mm; i.e., dime to nickel size) – Follow Allergist's written instructions (e.g., continue to advance).

- **"B"** (swelling 20 – 25 mm; i.e., nickel to quarter size) – Follow Allergist's written instructions (e.g., repeat last dose given)

- **"C"** (swelling persisting more than 12 hours or over 25mm; i.e., quarter size or larger) – Follow Allergist's written instructions (e.g., decrease dosage by 1 dose).

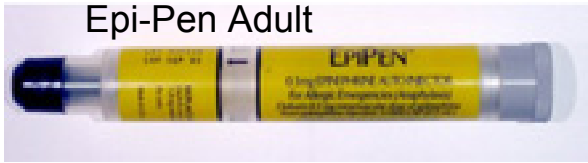
- Systemic reactions (hives, sneezing, itching, asthma, difficulty breathing, or shock) – Immediate care/action, then follow Allergist's written instructions.
  - Generally, the subsequent allergen extract dose is reduced to 1/3 of the last dose that did not cause a reaction and repeated 3 times before advancing per schedule.
- If the injections cause repeated reactions or are suspected of causing repeated delayed symptoms, or if reactions prevent progression of treatment, contact the Allergist for further instructions.

Treatment of Local Reactions

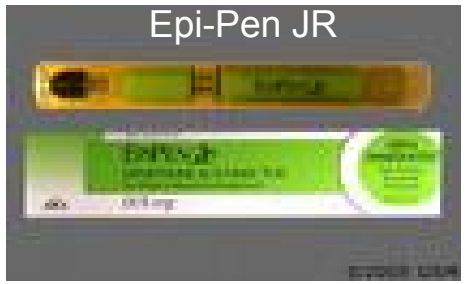
- Apply hydrocortisone (topical steroid)
- Apply ice to site
- Non-steroidal anti-inflammatory drugs (NSAIDS) to reduce swelling
- Take oral antihistamine (Benadryl, Allegra, etc.)
- Non-prescription pain-relievers (acetaminophen) to relieve pain

Treatment of Anaphylaxis

Epi-Pen Adult



Epi-Pen JR



TwinJect

- Notify the physician!
- May be controlled by immediately placing a tourniquet above the injection site
- Giving up to 0.01 ml/kg of 1: 1000 epinephrine up to 0.50 ml every 10-20 minutes subcutaneously.
- For the average adult, give 0.10ml of 1:1000 epinephrine subcutaneously in the injection site and 0.2ml of 1:1000 epinephrine in the other arm or inject 0.3mg EpiPen / TwinJect auto injector intramuscularly into the anterolateral aspect of the thigh.
- For children, administer 0.15mg EpiPen/TwinJect IM into the thigh.

AIT CHECKS

- **Expiration Dates:**
  - **Vials 1-3 (Silver, Green, Blue) = 6 MONTHS FROM DATE OF RECONSTITUTION**
  - **Vials 4-5 (Gold, Red) = 1 YEAR FROM DATE OF RECONSTITUTION**

  ***Expiration dates on vials 1-4 (Silver-Gold) must not exceed expiration date on vial 5 (Red).**

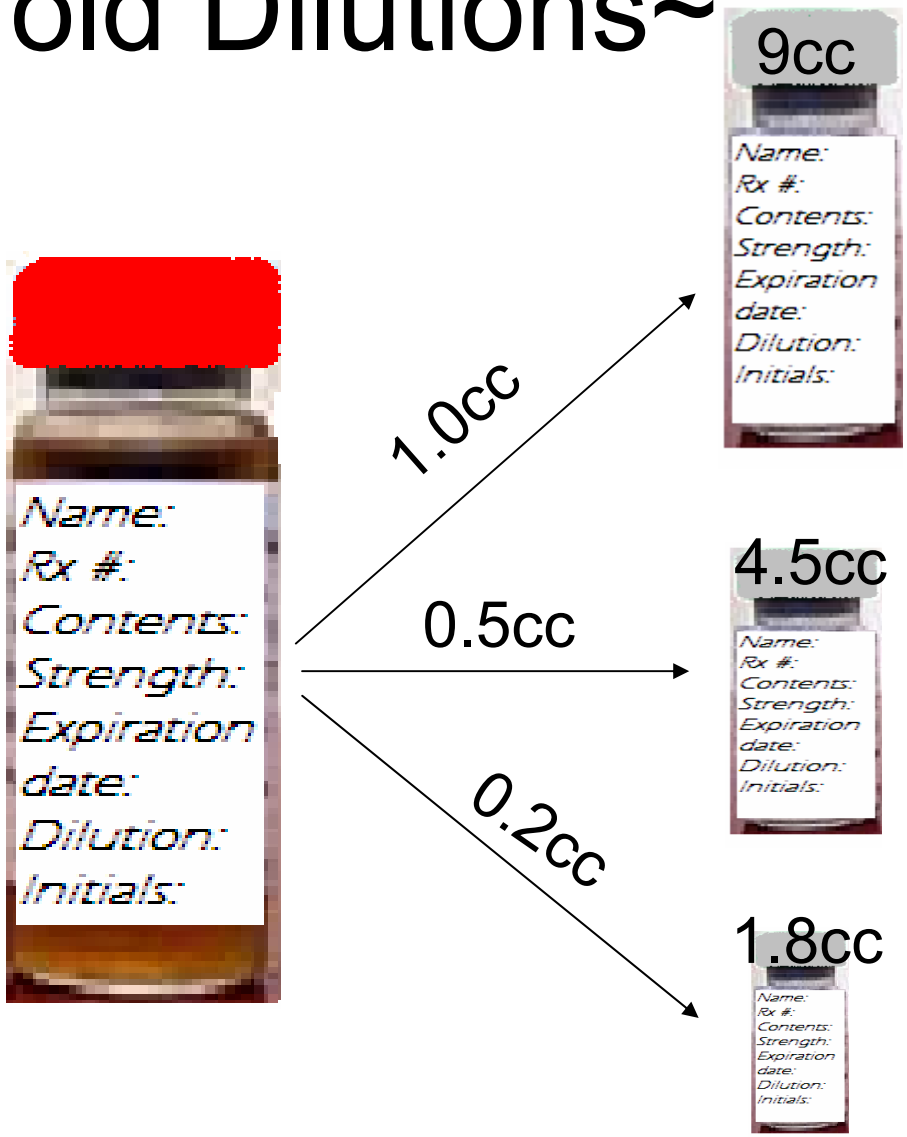
- Vial is good for 6 months if concentration is < 1:1000 w/v
- Vial is good for 1 year if concentration is ≥ 1:1000 w/v

How to dilute from available vials:

- Example: To make vial #4 from vial #5:
  - Equipments needed –
    - 1cc syringe/needle
    - 9cc Sterile Albumin Saline vial (from WRAMC extract lab)
  - Draw up 1cc of extract from vial #5 and inject into a 9cc Sterile Albumin Saline vial (extract diluent)
  - Mix well to make a 1:10 v/v dilution
  - Label the newly made vial #4 with the following:
    - Patient's name & SSN
    - Prescription number
    - Extract contents (abbreviations)
    - New concentration & vial color (as will not have proper cap)
    - Expiration date

~Making 10-fold Dilutions~

- To 9 cc Sterile Albumin Saline vial- draw up 1.0cc of extract and inject into new vial.
- To 4.5 cc Sterile Albumin Saline vial- draw up 0.5 cc of extract and inject into new vial.
- To 1.8 cc Sterile Albumin Saline vial- draw up 0.2 cc of extract and inject into new vial.



Example of Dilutional Strengths

Vial	v/v	W/V	AU/ML	BAU/ML
5 Red	1:1	1:100	2000	7750
4 Gold	1:10	1:1,000	200	775
3 Blue	1:100	1:10,000	20	77.5
2 Green	1:1000	1:100,000	2	7.75
1 Silver	1:10,000	1:1,000,000	0.2	.775

Venom Extract Dilutions:

(follow manufacturer's dilution instruction for maintenance vial)

****For further VIT dilutions, follow same protocol for AIT dilutions above****

Strength	Expiration **from date of dilution**
100mcg/ml or 300mcg/ml	6 months **(not to exceed manufacturer's expiration date)**
10mcg/ml or 30mcg/ml	30 days
1mcg/ml or 3mcg/ml	30 days
0.1mcg/ml or 0.3mcg/ml	14 days
0.01mcg/ml or 0.03mcg/ml	1 day (24 hours)
0.001 mcg or 0.003mcg/ml	1 day (24 hours)

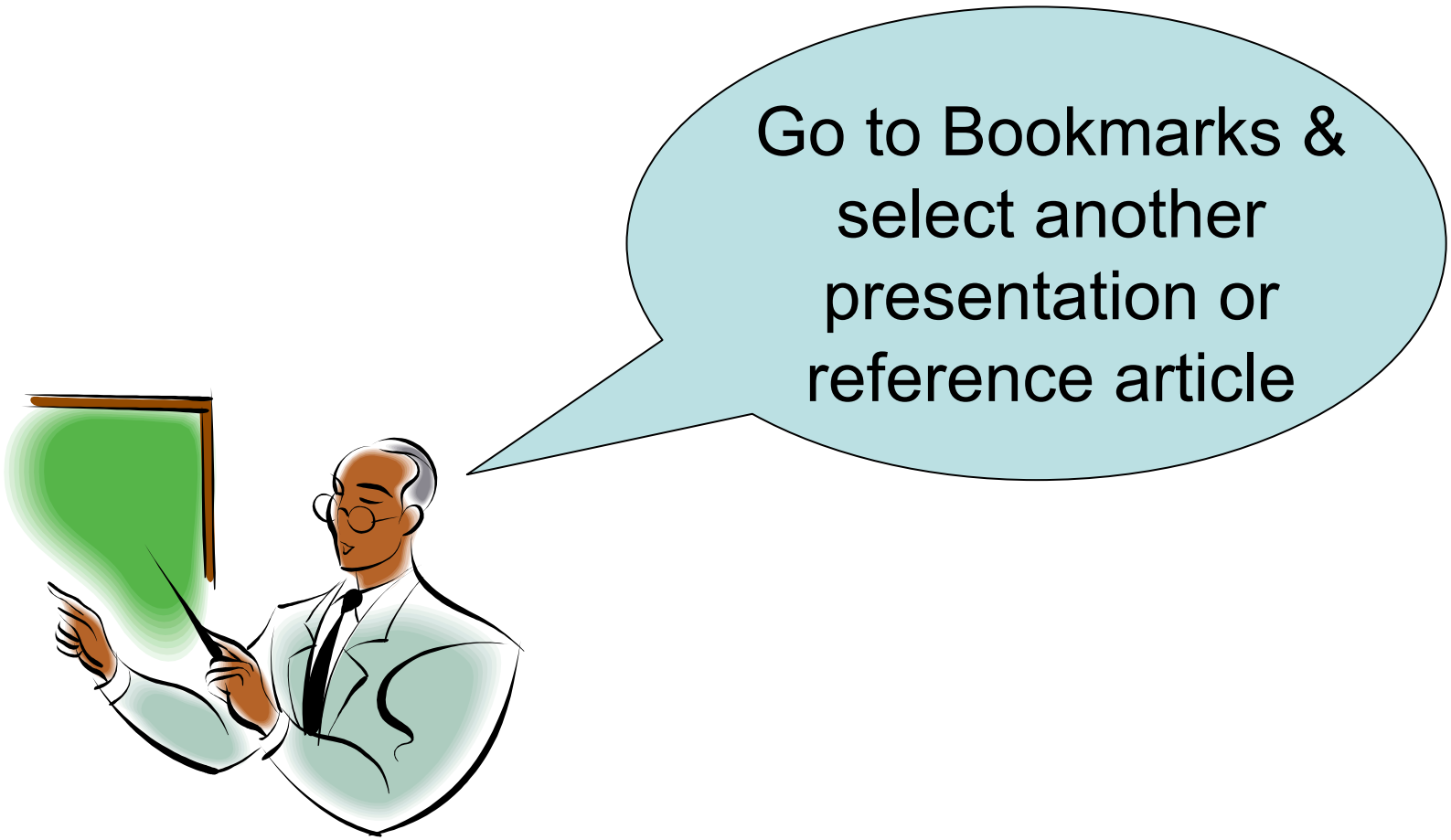
Summary

- Pull the patient's allergy record.
- Pull the patient's extract. Ensure that the right extract is pulled for the right patient, that the vial content agrees with what is ordered.
- Question the patient about any delayed local reaction or systemic symptoms. Make the appropriate adjustment in the dosage IAW protocol guidelines. If the patient states he or she had a delayed systemic symptoms, record this on the injection administration record and make a follow up appointment with the Allergist for the patient to be seen before proceeding with immunotherapy.
- Check dosage progression schedule for the amount of extract to be given. Document the dosage in the appropriate column on the injection record. The technician who is administering immunotherapy will initial the appropriate areas on the treatment record. Annotate the date and time of administration, and the injection site.
- Gently shake the vial before using. Draw up the dosage required using 1cc or 3cc syringe with a 26 - 27 gauge (5/8 – ½ inch) safety needle. Change the needle prior to injection. Ensure that the pertinent information is checked: confirm this information with the patient.
    (1) Right patient
    (2) Right extract
    (3) Right dosage
    (4) Right interval
    (5) Right method or technique

Summary (cont.)

- Administer the allergy injection. Give the injection subcutaneously into the posterolateral surface of the middle third of the upper arm. Always pull back on the plunger before the allergy extract is administered; if blood returns, withdraw the needle and use the other arm. Avoid massaging the injection site to lessen unduly rapid absorption of the allergen.
- Instruct the patient to wait 30 minutes in the patient waiting area and to report any problems immediately.
- Check the injection site(s) prior to the patient leaving the clinic.
- Document all reactions in the patient's allergy record. Notify the Physician In Charge and the Allergist if there are recurrent local reactions limiting advancement of the allergy shot or any systemic reactions or other problems.
- Unless reactions dictate a change in dosage and/or the Allergist annotates otherwise, the technician will always follow the prescribed schedule on the Allergen Extract Prescription Form. Any questions will be directed to the Allergist before administering a shot.
- No patient will be permitted to administer their own injections. Only the Allergist may determine if patient may receive their injections at another location. summation

End of Selection



Optimizing the Safety of Immunotherapy Administration Outside of the Prescribing Allergist's Office

I. Immunotherapy overview:

Definition: *Allergen Immunotherapy is a treatment aimed at modifying the allergic disease through a series of injections of a mixture of aeroallergen extracts composed or clinically relevant allergens identified during the allergy evaluation*

1. Immunotherapy has been shown to be effective in multiple controlled studies for the treatment of allergic rhinitis, asthma and stinging insect venom hypersensitivity
2. Potential prophylactic treatment: may prevent the development of new allergies or progression from allergic rhinitis to asthma

II. Immunotherapy potential mechanisms*: Immunologic changes during immunotherapy are complex. Successful immunotherapy is often associated with a shift from TH2 to TH1 CD4 lymphocyte immune response to allergen.* Immunotherapy induces a number of immunologic changes. Studies over several seasons of immunotherapy show that the usual seasonal rise of IgE is blunted by immunotherapy. On the other hand, it is believed that IgG protective "blocking antibody" production is stimulated by immunotherapy. However, these changes in IgE and IgG may not correlate with clinical efficacy. Immunotherapy inhibits the early and late phase responses, which results in decreased inflammation. Partial desensitization may play a role in immunotherapy. Immunotherapy may also induce production of "regulatory" T cells (CD4+CD25+) which may produce factors (IL-10and/or TGF-β) to down-regulate allergic immune responses. Clinically effective immunotherapy may be the result of some or all of these mechanisms.

III. Indications and Contraindication for Allergen Immunotherapy

1. Candidates: Patients with allergic rhinitis and/or asthma* with symptoms after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE poor response to pharmacotherapy and/or allergen avoidance and 1 of the following [1]

a. Unacceptable adverse effects of medications

b. Desire to reduce or avoid long-term pharmacotherapy and the cost of medication.

c. Coexisting allergic rhinitis and asthma

d. Immunotherapy may prevent the development of asthma in patients with allergic rhinitis

e. Immunotherapy may prevent the development of new allergen sensitivities

2. Patients who are not allergen immunotherapy candidates: *Medical conditions that reduce the patient's ability to survive a systemic reaction are relative contraindications for allergen immunotherapy.* [1]

a. Medical conditions that reduce the patient's ability to survive a systemic reaction are relative contraindications for allergen immunotherapy such as severe coronary artery diseases

b. Patients who are mentally or physically unable to communicate clearly with the allergist

c. Patients who have a history of noncompliance

d. Cautious attitude in prescribing immunotherapy to patients on beta-blocker medications.

e. Pregnancy (do not initiate therapy in newly pregnant women but can continue in those already on immunotherapy)

IV: Immunotherapy protocol [2]

• **Build-up phase**: involves receiving injections with increasing amounts of the allergens. The frequency of injections during this phase generally ranges from 1 to 2 times a week, though more rapid build-up schedules are sometimes used. The duration of this phase depends on the frequency of the injections but generally ranges from 3 to 6 months (at a frequency of 2 times and 1 time a week, respectively).

• **Maintenance phase:** This phase begins when the effective therapeutic dose is reached. The effective therapeutic dose is based on recommendations from a national collaborative committee called the Joint Task Force for Practice Parameters: Allergen Immunotherapy: A Practice Parameter 2003 and was determined after review of a number of published studies on immunotherapy. The effective maintenance dose may be individualized for a particular person based on their degree of allergen sensitivity (how 'allergic they are' to the allergens in their vaccine) and their response to the immunotherapy build-up phase. Once the maintenance dose is reached, the intervals between the allergy injections can be increased. The intervals between maintenance immunotherapy injections generally ranges from every 2 to every 4 weeks but should be individualized to provide the best combination of effectiveness and safety for each person. Allergists may consider several factors in determining maintenance injection frequency including degree of symptomatic control at a particular maintenance interval and reactions from allergy injections. Shorter intervals between allergy injections may lead to less reactions and greater efficacy in some people.

V. Allergen Immunotherapy Safety:

1. Risk factors for allergen immunotherapy [3]

a. Error in dosage
b. Presence of symptomatic asthma
c. High degree of allergen hypersensitivity
d. Use of beta-blockers
e. Injections from new vials
f. Injections given during periods when symptoms are exacerbated

2. Allergen immunotherapy local and systemic reactions

a. Local reactions common

b. Incidence of systemic reactions (SR) with conventional immunotherapy schedules in the published literature for combined build-up and maintenance phase ranged from:[3] 0.05% - 3.2 % per injection or 0.84% to 46.7% of patients (mean 12.92%, SD 10.8 % of pts)[4]

3. Treatment of Immunotherapy Adverse Reactions

a. Local reactions common occurrence: redness, swelling and heat at injection site

i. If persistent large local reaction consider:

1. Pre-medication with H1 blockers
2. Decreasing dose or rate of build-up

b. Systemic reactions: the recommendations for epinephrine administration are derived from the most recent practice parameters for treatment of anaphylaxis[9]

i. Epinephrine 1:1000 w/v

1. Adults: 0.2 to 0.5ml intramuscularly (IM), preferably the thigh or subcutaneously (SQ) into the arm (deltoid) every 5 minutes, as needed to control symptoms and raise blood pressure
2. Children: 0.01ml/kg (max 0.3 mg dosage) every 5 minutes as needed to, as needed to control symptoms and raise blood pressure
3. Alternately, an epinephrine autoinjector (e.g., EpiPen™ or EpiPen Jr™ or TwinJect™) can be administered through clothing into the lateral thigh.
4. Do not use crash cart injectables in pre-filled syringe, which are 1:10,000 wt/v and indicated for intravenous (IV) use
5. Location of injection: arm permits easy access for administration of epinephrine, although intramuscular injection into the anterolateral thigh produces higher and more rapid peak plasma levels compared with IM or SQ injections in the arm.[9]

ii. Other interventions:

1. H1 antihistamines: diphenhydramine IM or IV
   a. Adults: 25 to 50 mg
   b. Children: 1-2 mg/kg
2. H2 blockers p.o. or IV (cimetidine, ranitidine, famotidine) – for epinephrine – resistant hypotension
3. Intravenous fluids or vasopressors as needed for vascular collapse
4. Consider glucagon if patient on beta-blocker
5. Maintain the airway

iii. Call prescribing allergists for further instructions before administering another allergy injection after a patient has had a systemic reactions

4. Allergen Immunotherapy Administration Supervision: appropriate setting, personnel and equipment.

Allergen immunotherapy should be given in settings where emergency resuscitative equipment and trained personnel are immediately available to treat systemic reactions under the supervision of a physician or licensed physician extender[6]

The trained personnel should be familiar with the following procedures:

a. Adjustment of dose of allergen immunotherapy extract to minimize reactions.
b. Recognition and treatment of local and systemic reactions to immunotherapy injections.
c. Basic cardiopulmonary resuscitation.
d. Ongoing patient education in recognition and treatment of local and systemic reactions that occur outside the physician's office.

Equipment

a. Stethoscope and sphygmomanometer.
b. Tourniquet, syringes, hypodermic needles (14-gauge) and large bore needles.
c. Aqueous epinephrine HCL 1:1000.
d. Equipment to administer oxygen by mask.
e. Intravenous fluid set-up.
f. Antihistamine.
g. Corticosteroids for intravenous injection.
h. Vasopressor
i. Oral airway.
j. Equipment to maintain an airway appropriate for the supervising physician expertise and skill**.**

5. Immunotherapy Administrations documentation: what you should receive and record

A full, clear, and detailed documentation of the patient's immunotherapy schedule must accompany the patient when he or she transfers from one physician to another. Also, a record of previous responses to and compliance with the program should be communicated to the new physician. Finally, a detailed record of the results of the patient's specific- IgE antibody tests (immediate-type skin tests or in vitro tests) should be provided.[1]

6. Allergy Extract Nomenclature: Recommended Dilution Labeling, Color-Coding and Vial Nomenclature[1]

Unfortunately, there is considerable diversity in the allergy extract nomenclature in US and this may lead to confusion and administration errors in outside offices particularly if they supervise immunotherapy from several offices with different nomenclature systems. The Joint Task Force On Practice Parameters developed

a proposed uniform nomenclature system with the goal to have this system eventually adopted by all practicing US allergists. Number 1 vial is color coded red and called the 1:1 v/v dilution or maintenance concentrate. The subsequent dilutions are colored and named as below. However not all practices have adopted this standard nomenclature and therefore it is very important for you to review the, labeling nomenclature from each office that you receive allergy immunotherapy vaccines.

Dilution from maintenance	Dilution designation in volume per volume (V/V)	Number	Color
Maintenance	1:1	1	Red
10-fold	1:10	2	Yellow
100-fold	1:100	3	Blue
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

7. Administration Form Information:

- Patient name, date of birth and telephone number
- Prescribing physician with practice demographics
- Vaccine name and dilution from maintenance in volume per volume, bottle letter, color and number (if used)
- Expiration date of all dilutions
- Date of injection
- Arm injection administered
- Delivered volume reported in milliliters
- Immunotherapy schedules
- Injection reactions: to be used to document local or systemic reactions
- Health screen - Verbal or written interview of patient to evaluate patient's health status prior to administering the allergy vaccine
- Peak expiratory flow rate (PEFR); In patients with asthma (unstable asthma in particular), peak expiratory flow rate measurements should be obtained before each injection. If done repeatedly over time, this permits better determination of baseline peak expiratory flow rate and variability. PEFR variability, the difference in peak expiratory readings taken at different times, has a diurnal pattern with the lowest reading usually in the morning. Normal PEFR variability is <20%, If a

patient's peak expiratory flow rate is 20% below baseline, the clinical condition of the patient should be evaluated before administration of the injection.

- Obtain peak flow measurement in asthmatic patients before administering
- If 20 % below best baseline withhold allergy injection until further evaluation

• **Antihistamine use**: Ask whether the patient has taken an antihistamine that day to improve consistency in interpretation of reactions:

- **May reduce adverse reactions**: a concern with the use of premedication is that it may mask milder systemic reactions allowing the build-up to proceed to a subsequent more serious systemic reaction. To the contrary, the published literature on studies utilized accelerated schedules for inhalant and venom allergen immunotherapy have demonstrated less incidence of local and systemic reactions with antihistamine premedication[6,7]

VI. Allergen Immunotherapy Administration Supervision: practical tips to enhance safety

1. Review all documents carefully
2. Inspect the allergy vaccine vials and familiarize yourself with the nomenclature and dosing schedule
3. Vials in transit should be not be exposed to temperature extremes (freezing or extreme heat) because this could decrease extract potency
4. Storage of allergy vaccine vials: keep refrigerated at 4° .Prolonged exposure of allergy vaccine vials to room temperature over time may diminish extract potency: one study found loss of potency pollen extracts exposed to room temperature for 13 hours a week for longer than 3 months[8]
5. Do not administer injection unless you have written verification of the last injection dose and date
6. Interview the patient about current health status including medication changes
7. Have the patient wait in the office for 30 minutes after the injection and instruct them to immediately report to the staff any symptoms suggestive of an allergic reaction.

Do not hesitate to contact prescribing allergist if you have ANY questions or concerns!

VII. Allergen immunotherapy adverse reactions: measures that can minimize the risk:

Serious reactions to immunotherapy are uncommon. Appropriate safety measures based on the known risk factors may prevent or reduce incidence of serious reactions.

Risk factors for immunotherapy and some measures that may help prevent include:

1. Error in dosage: check and double-check: vials, patient name and dosing record, have patient confirm vials
2. Presence of symptomatic asthma: do not administer injection until asthma stabilize
3. High degree of hypersensitivity: consider premedication, consult prescribing allergists if recurrent and persistent large local reactions
4. Use of beta-blockers: ask about new medications each visit

5 Injections from new vials: dosage adjustment per prescribing allergist

6. Injections made during periods of exacerbation of symptoms: consider consulting prescribing allergist before administering

Remember: *Take your time and review the records to ensure that:*

You are giving the right dose of the right allergy immunotherapy vial to the right patient because….

No patient ever died from an allergy shot waiting to receive the injection …

The extra time and wait will not harm you or the patient but dosing errors and allergy injections to actively symptomatic patients may seriously harm

References For Optimizing The Safety Of Immunotherapy Administration Outside Of The Prescribing Allergist's Office

1. Li JT et al Joint Task Force On Practice Parameter: Allergen immunotherapy: A practice parameter. Ann Allergy Asthma Immunol 2003; 90(suppl).
2. What are "Allergy Shots?" Tips to Remember are created by the Public Education Committee of the American Academy of Allergy, Asthma and Immunology. This brochure was updated in 2003 available at AAAAI website (www.aaaai.org) http://www.aaaai.org/patients/publicedmat/tips/whatareallergyshots.stm
3. Bousquet J., Lockey R., Malling H.J. WHO Position Paper Allergen immunotherapy: therapeutic vaccines for allergic diseases Allergy Eur. J of Allergy Clin Immunol 1998; Number 44 Volume 53
4. Stewart GE, Lockey, RE: Systemic reaction to Allergen Immunotherapy, J Allergy and Clin Immunol 1992:90; 567-78.
5. Position Statement on administration of immunotherapy outside of the prescribing allergist facility. Drug and Anaphylaxis Committee of ACAAI. Ann Allergy Asthma and Immunol 1998;81:101-102
6. Muller U, Hari Y, Berchtold E, Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. J Allergy Clin Immunol 2001;107 (1):81-861

7. Neilson L, Johnsen C, Mosbech H, Poulsen L, Malling H Antihistamine premedication in specific cluster immunotherapy: A double-blind-placebo controlled study. J Allergy Clin Immunol 1996; 97 (6): 1207-13
8. Nelson HS Effect of preservatives and conditions of storage on the potency of allergy extracts J Allergy Clin Immunol. 1981 Jan; 67(1):64-9
9. Lieberman P et al The Diagnosis &Management of Anaphylaxis: An updated Practice J Allergy Clin Immunol 2004; 115 (3) (supplement)

Other suggested references:

Efficacy

a. Durham et al. Long-term Clinical Efficacy of Grass-pollen Immunotherapy New England Journal of Medicine 1999;341 468

Possible preventive effect of allergen immunotherapy

a. Des Roches A, Paradis L, Menardo J-L, et al. Immunotherapy With A Standardized Dermatophagoides Pteronyssinus Extract VI. Specific Immunotherapy Prevents The Onset of New Sensitizations In Children. J Allergy Clin Immunol 1997; 99;450-3.
b. Rurello-D'Ambrosio et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001; 31: 1295-1302
c. Panjno, GB et al. Prevention of new sensitization in asthmatic children monsensitized to house dust mites by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001; 31:1392-7
d. Jacobsen L Dreberg S, et al. Immunotherapy as a Preventive Treatment (Abstract) J Allergy Clin Immunol 1996;97: 232
e. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. Respir Res 2005 6:153.

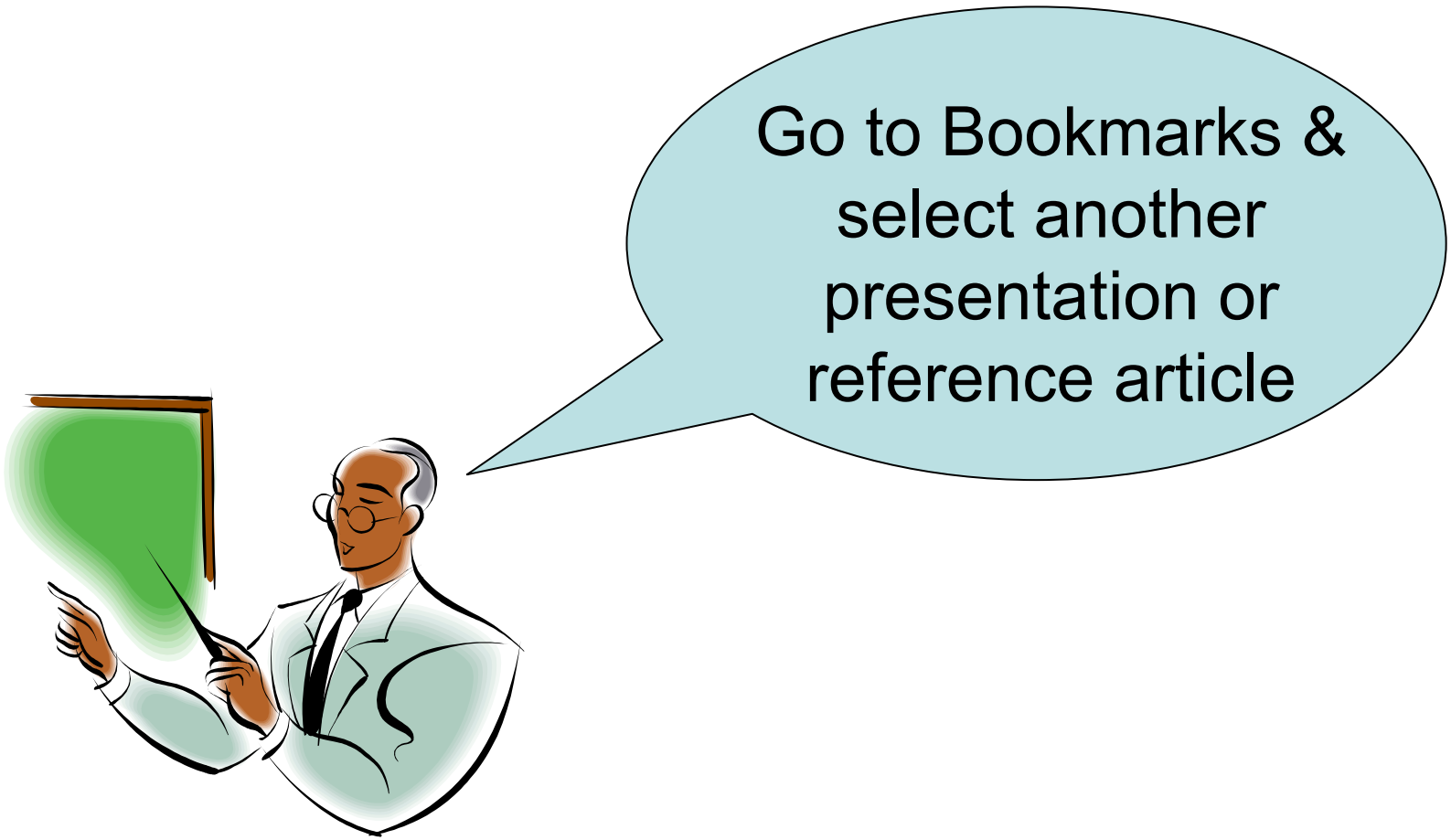
Adverse reactions: treatment

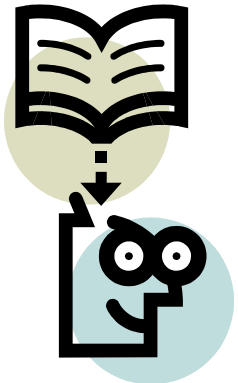
a. Simons F, Roberts J, Gu X, Simons K. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998; 33-34.
b. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 2005 Mar;115 (3 Suppl 2):S483-523.

Systemic Reactions and Immunotherapy Fatalities

a. Lockey RF, Benedict LM, Turkeltaub PC, and Bukantz SC J Allergy Clin Immunol 1987; 79: 660-77
b. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TAE. J Allergy Clin Immunol 1993; 92: 6-15
c. Bernstein D, et. al. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001 J Allergy Clin Immunol 2004;113:1129-36.)

End of Selection





Click the ☒ next to the heading to view the administrative material.

Documentation of allergen immunotherapy

Documentation of Informed Consent

Informed consent is a process by which a patient and physician discuss various aspects of a proposed treatment. A copy of the signed written consent form and any entries pertaining to the consenting process before the immunotherapy was initiated is/are required. The consent process usually consists of a record of the following:

- Treatment proposed and its alternatives
- Benefits expected from the treatment
- Risks, including a fair description of how frequently adverse outcomes (including death) occur
- Anticipated duration of treatment
- Office policies that affect treatment

Immunotherapy Content Form

The purpose of this form is to define the contents of the vaccine in enough detail that it could be duplicated if necessary.

This form should include the following:

- Appropriate patient identifiers, including name, social security number, and birth date
- Vaccine contents, including common name or genus and species of individual allergens and a description of all mixtures
- Prescription number (USACAEL)
- Volume of individual components and final concentration of each
- Type of diluent used (if any)
- Immunotherapy expiration date (for each vial)

Immunotherapy Vaccine Administration Form

This form should be used to document the administration of vaccine to a patient. Its design should be clear enough so that the person administering an injection is unlikely to make an error in administration. It also should permit documentation in enough detail to allow later determination of what was done. The form should contain the following:

- Appropriate patient identifiers, including name, social security number, and birth date. Placement of the patient's picture on the form may be helpful, particularly when more than 1 patient has the same name. If 2 or more patients have the same name, that fact should be noted on the form as well, as should a means of distinguishing the 2 individuals.
- Name of the vaccine, including an indication of the dilution from the maintenance concentrate in volume per volume. Other identifiers, such as cap color, number, or letter, may help to reduce the risk of an administration error.
- Dates and times of vaccine injection
- Volume of vaccine administered in milliliters (mL) with each injection. During the buildup phase, the dose can be determined using a standard (provided) schedule.
- Arm in which the injection was given (left or right). This may facilitate determination of which vaccine causes local reactions. Because local reactions do not correlate reliably with systemic reactions, the presence of an immediate local reaction may not be a useful way to determine which vaccine caused a systemic reaction. Although it is

a common practice to alternate the arm into which a particular vaccine is given, there is no evidence that this is necessary.

- In patients with asthma (unstable asthma in particular), peak expiratory flow rate measurements may be considered before an injection. If a patient's peak expiratory flow rate is significantly below baseline, the clinical condition of the patient should be evaluated before administration of the injection.
- Description of any reactions. Dose adjustments may be necessary if reactions are frequent or severe.
- Details of any treatment given in response to a reaction should be documented in the medical record and referenced on the administration form.
- Any adjustment from the standard schedule and the reason for the adjustment (e.g., missed appointments).
- Clinical status of the patient before the injection. In general, patients who have high fever or any significant systemic illness should not receive an injection. It is desirable to document the patient's clinical condition before each injection, particularly if the patient is symptomatic.
- Whether the patient has taken an antihistamine that day
- Whether any new medication has been taken since the last immunotherapy injection

Labels for Vaccine Vials

Each vial of vaccine should be labeled in a way that permits easy identification. Each label should include the following information:

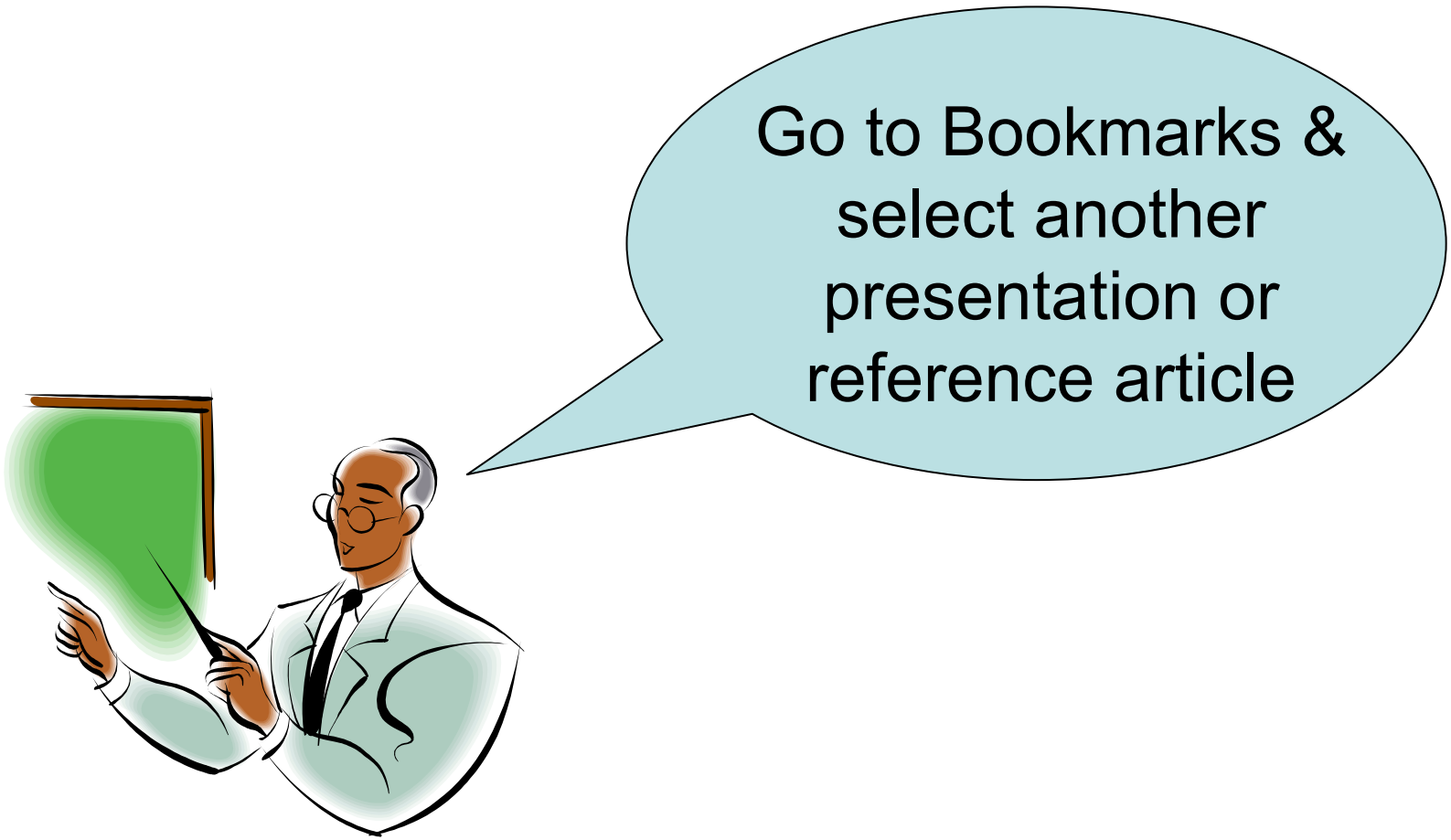
- Appropriate patient identifiers, including patient name, prescription or social security number, or birth date
- General description of the vaccine contents. Because of space limitations, it may be necessary to abbreviate the antigens. Possible abbreviations are as follows: tree, T; grass, G; bermuda, B; weeds, W; ragweed, R; mold, M; *Alternaria*, Alt; *Cladosporium*, Cla; *Penicillium*, Pcn; cat, C; dog, D; cockroach, Cr; dust mite, DM; *D. farinae*, Df; *D. pteronyssinus*, Dp; mixture, Mx. A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate in volume per volume. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- Vaccine expiration date

Instruction Form for Use at an Outside Facility

An instruction form should accompany all patients who go to an outside facility for immunotherapy injections. It should include:

- General instructions for administration of immunotherapy
- Directions for adjusting the dose if there is a reaction
- Directions for adjusting the dose after an unexpected interval between injections
- Instructions for treating reactions if they occur
- Name and contact information of the prescribing Allergist.

End of Selection



ALLERGY IMMUNOTHERAPY (AIT) PROBLEM LIST / PATIENT QUESTIONNAIRE

AIT Start Date:_____ Information Reviewed:_____, _____, _____, _____

Patient Name _____ Phone (H) _____
SSN:_____
Address (W) _____
_____ Fax # _____
_____

Next of Kin Phone (H) _____
Emergency Contact _____ (W) _____

Primary Care Physician _____ Phone # _____

Prescribing Allergist _____ Phone # _____

PROBLEM LIST

Please check any of the following medical problems if applicable:

- ☐ Allergic rhinitis / hay fever
- ☐ Asthma
- ☐ Diabetes (sugar problems)
- ☐ Immunodeficiency
- ☐ Coronary Artery Disease
- ☐ Emphysema
- ☐ Migraines
- ☐ Cancer
- ☐ Sinusitis
- ☐ Neurological problems (i.e. seizures)
- ☐ Eczema
- ☐ Stroke
- ☐ High Blood Pressure
- ☐ Restrict shots to L/R arm only

Please list any other medical problem not listed above:

CURRENT MEDICATIONS

Please list all medications (name and dose) that you are taking to include prescription, over-the-counter, and herbal formulations, vitamins and food supplements:

Do you take any of the following?

- Nonsteroidal anti-inflammatory medications (pain, arthritis, anti-inflammatory)

☐ Aspirin ☐ Indomethacin ☐ Oxaprozin ☐ Naproxen ☐ Nabumetone
☐ Ketoprofen ☐ Piroxicam ☐ Diclofenac ☐ Ketorolac ☐ Trilisate
☐ Salsalate ☐ Diflunisal ☐ Meclofenamate ☐ Sulindac
☐ Etodolac ☐ Tolmetin ☐ Flurbiprofen ☐ Ibuprofen

- Beta-Blockers (heart disease, high blood pressure, glaucoma)

☐ Acebutolol ☐ Carvedilol ☐ Pindolol ☐ Atenolol
☐ Laberalol ☐ Propranolol ☐ Betaxolol ☐ Metoprolol
☐ Timolol ☐ Bisoprolol ☐ Nadolol ☐ Cartcolol

- ACE inhibitors / Angiotensis Receptor Blockers (High blood pressure, kidney)

☐ Benazepril ☐ Lisinopril ☐ Ranipril ☐ Captopril
☐ Losartan ☐ Trandolapril ☐ Enalapril ☐ Moexipril
☐ Fosinopril ☐ Quinapril

- Corticosteroids (pills, liquids, or shots)

☐ Betamethosone ☐ Hydrocortisone ☐ Prednisone ☐ Cortisone
☐ Triamcinolone ☐ Methylprednisolones ☐ Dexamethaxone ☐ Prednisolons

DRUG ALLERGIES

Please list any allergies or adverse reactions to any medications that you may have:

GENERAL QUESTIONS

Please circle the best answer for each of these questions concerning your allergy shots:

1. During the last year my symptoms on allergy shots have:
   a) worsened b) stayed the same c) improved d) disappeared completely e) don't know

2. How many times have you visited a health care provider for allergy problems in the last year (not including allergy shot visits)?
   0 1 2 3 4 5 6 7 8 9 10 >10

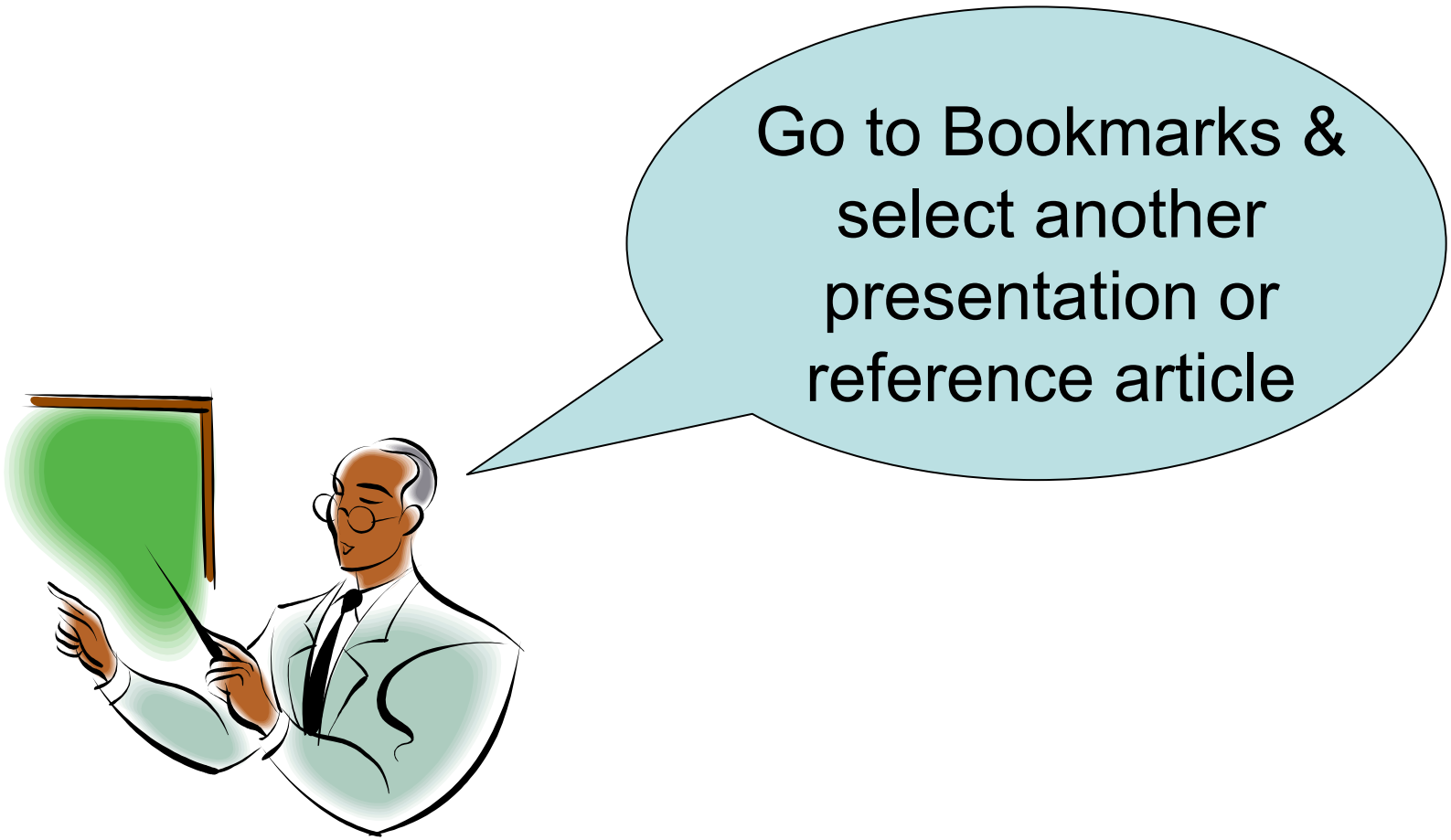
3. How many workdays were missed during the last year that were all or partly due to allergies?
   0 1 2 3 4 5 6 7 8 9 10 >10

4. Comments:_____

_____

Reviewed by Physician:_____ Date:_____

End of Selection



MEMORANDUM FOR: Allergy Immunotherapy Patients

SUBJECT: Allergy Patient Consent / Instruction Sheet

1. As a service to our patients, the _____ clinic administers Allergy Immunotherapy (AIT) for pollens, molds, and animal dander, and stinging insects as directed by your Allergist.

2. An Allergy specialist must evaluate your medical condition, prescribe a course of AIT, and supply the allergen extract vials. Your first shot of any new prescription must be given at your Allergist's office. The site for the first shot of a refill vial will be at your Allergist’s discretion.

3. We will maintain your allergen vials in our medication refrigerator. This will ensure your extract is maintained at the proper conditions. All vials must be labeled with name, vial number or v/v concentration, prescription number, contents, and expiration date in accordance with ACAAI standards of care.

4. Before treatment begins, you will be required to have a completed AIT patient questionnaire on file.

5. "Allergy shots" will be given in room _____, on weekdays from 9:00-11:00 and 1:00-3:00 [modify times as appropriate]. A fully credentialed health care provider and nurse must be present to administer your allergy shots. Availability of Medical staff may be limited on rare occasions due to other primary duties, and you may not be able to receive your shot. A brief delay in receiving your AIT will not pose a health risk, but may result in a subsequent dose adjustment.

6. You are receiving injections of the materials to which you are most allergic. You may have very significant local or generalized reactions that require prompt treatment.

7. Nearly all of the serious and rapidly progressive reactions begin within 30 minutes after the shot.

8. **We require a 30 minute waiting period after all allergy injections.** You must wait in _____ after your injections and be checked by a staff member before leaving. If your schedule does not permit you to wait the required 30 minutes, you will not be able to receive your shot at that time.

9. Promptly inform the staff if you are having any significant increase in itching, hay fever, asthma, hives, shortness of breath, throat clearing, or other discomforts you did not arrive with.

10. Those patients having their doses increased towards maintenance are most likely to have reactions, but even long term patients occasionally have serious reactions.

11. Serious local or generalized reactions may require prompt treatment. If you should experience a serious reaction (hives, trouble breathing or swallowing) while in the clinic we will implement treatment as far as possible to stabilize or resolve the problem. Be aware that should this situation occur, you would be required to be observed for several hours to be sure that you do not develop a delayed reaction to your allergens requiring further treatment. You may be observed in this clinic, or you may be transferred emergently to a higher level of care for ongoing treatment depending on the severity of your reaction.

12. Should you have a history of systemic reactions, you need to inform the staff promptly. Please make the staff aware if you do not have an epinephrine autoinjector (Epi-Pen or TwinJect) or do not have a ready knowledge of when and how to use it.

13. If you should experience a delayed reaction after leaving the clinic, notify the staff on your next visit. This is required to assure that you receive the correct amount of extract and prevent worsening reactions.

14. **If you have started on any new medications, notify the staff immediately.** The medications we use to treat a severe allergic reaction may NOT work as efficiently if you are on a class of drugs known as beta-blockers or ACE inhibitors. This could be a life-threatening situation. If your primary physician feels you absolutely must be on beta blockers, your prescribing Allergist must review this fact with you and your primary care provider/specialist before we can continue your allergy shots.

15. Significant illness with fevers over 100 degrees, respiratory illnesses, and worsened asthma symptoms are all conditions that require you notify staff of before receiving your allergy shot. These conditions may precipitate serious reactions after allergy shots. It is best to wait until these conditions resolve or stabilize before continuing.

I understand the above information and will comply with the clinic policies.

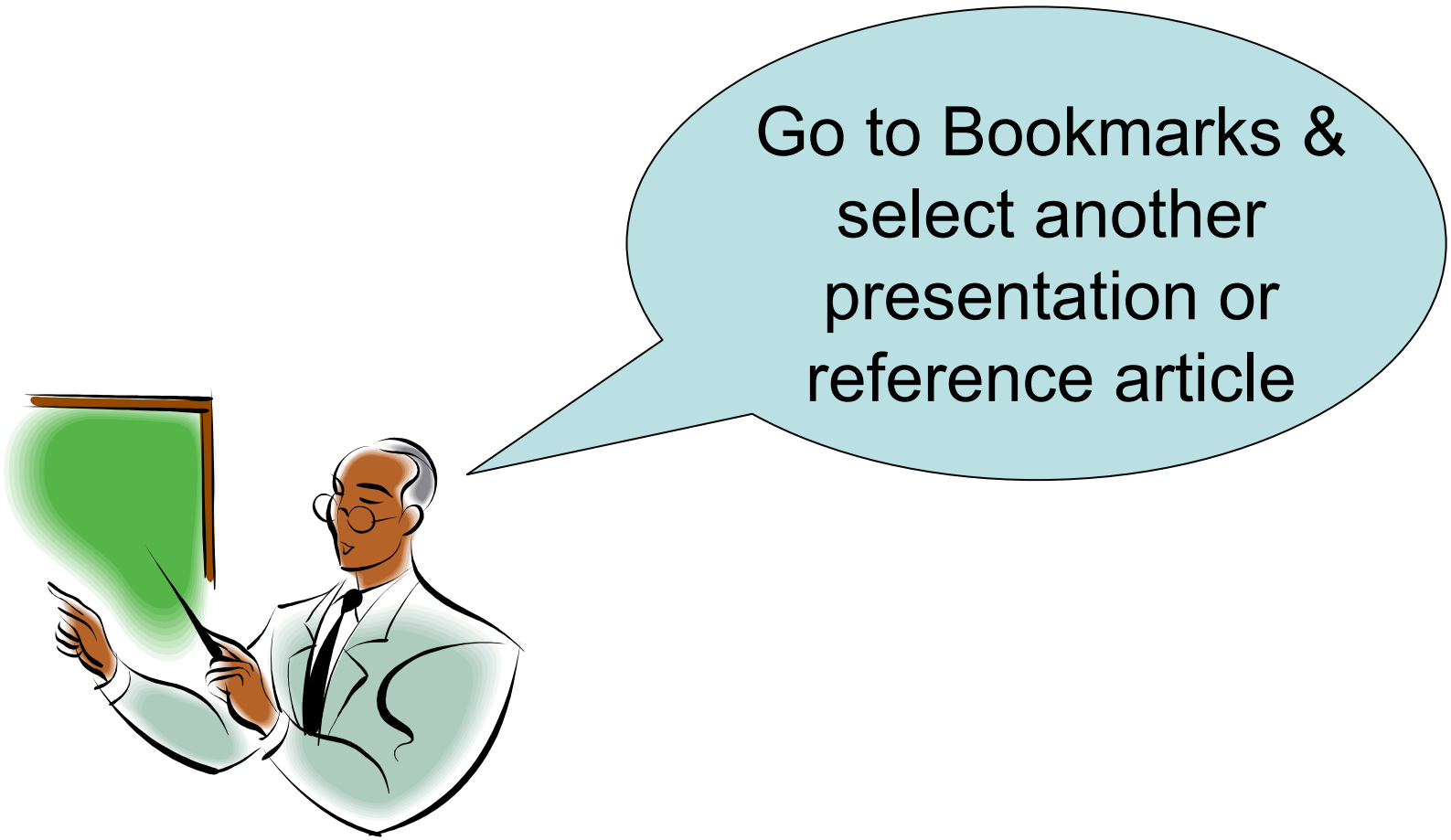
_____ _____

Patient's Signature Date

_____ _____

Witness Date

End of Selection



SPECIFIC INSTRUCTIONS

A. PHYSICIAN MUST ALWAYS BE IMMEDIATELY AVAILABLE IN THE CLINIC AREA.
B. ALL PATIENTS MUST REMAIN IN THE CLINIC AT LEAST 30 MINUTES AFTER AN INJECTION.
C. Use a **26-28** gauge needle and give the subcutaneous injection into the lower deltoid area.
D. Record data, dosage, and any reaction on a separate immunotherapy form.
E. GRADING AND MANAGEMENT OF REACTIONS:
   1. **Negative** (swelling up to 15 mm, i.e. dime size) – progress according to schedule.
   2. **"A"** swelling 15-20 mm, i.e. dime to nickel size) – repeat the same dosage.
   3. **"B"** (swelling 20-25mm, i.e. nickel to quarter size – return to the last dosage which caused no reaction.
   4. **"C"** (swelling persisting more than 12 hours or over 25mm, i.e. quarter size or larger – decrease dosage by 50%.
   5. **Systemic reactions** (hives, sneezing, generalized itching, asthma, difficulty breathing, or shock) may be controlled by immediately placing a tourniquet above the injection site, and giving up to **0.01 ml/kg of 1:1000 epinephrine**, up to 0.50 ml, every 10-20 minutes subcutaneously. NOTIFY THE PHYSICIAN. For the average adult, give **0.10** ml of 1:1000 epinephrine subcutaneously in the injection site and **0.20 ml** of 1:1000 epinephrine in the other arm. Generally the allergen extract dose is reduced to 1/3 the last dosage that caused no systemic reaction and repeated 3 times before increasing dose. If the injections cause repeated reactions or are suspected of causing delayed symptoms repeatedly, or if reactions prevent progression of treatment, please contact the medical facility below for further instructions.

F. IF THE PATIENT MISSSED THE SCHEDULED INJECTION BY:

Up to 7 days late, increased according to schedule	**22 to 28 days late,** reduce dose by 50%
8 to 14 days late, repeat the last dose	**29 to 42 days late,** reduce dose by 75%
15 to 21 days late, reduce dose by 25%	**43 to 56 days late,** reduce dose by 90%

In a patient with a history of previous shot reactions, severe asthma, or severe cardiac disease, the dose may need to be decreased even more. If in doubt, contact the medical facility below. If patient misses his/her scheduled injection by over 8 weeks, contact the medical facility below.

G. If newly informed that patient is pregnant or on beta-blockers, notify medical facility below for instruction.
H. **REFILL EXTRACT PRESCRIPTIONS.** When starting a new treatment vial, recommend a minimum of **50%** reduction in initial dose.

RECOMMENDED TREATMENT INSTRUCTION: Progress treatment using one vial at a time starting with the lowest numbered vial. When the schedule for each vial is completed, go to the next higher vial.

13. VIAL #	13 A. CONTENT W/V	CONTENT BAU/ML	CONTENT AU/ML	13B. DAYS BETWEEN SHOTS	13C. SCHEDULE (SEE BELOW)
1	1:2000000	1.1	0.2	3-7	A
2	1:200000	11	2	3-7	B
3	1:20000	110	20	3-7	C
4	1:2000	1,100	200	3-7	D
5	1:200	11,000	2,000	3-7	E

13D. When the maximum tolerated dose or a dose of _0.5___ ml of vial ___#5___ has been achieved, injections should be administered every __ ___2-4_____weeks. An exception to this is during the period of 1st year of AIT when injections should be administered every __1-4__weeks.

SCHEDULE A	SCHEDULE B	SCHEDULE C	SCHEDULE D	SCHEDULE E		SCHEDULE F/CUSTOM SCHEDULE
0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.05 ml	0.30 ml	
0.10 ml	0.10 ml	0.10 ml	0.10 ml	0.07 ml	0.35 ml	
0.25 ml	0.20 ml	0.20 ml	0.15 ml	0.10 ml	0.40ml	
0.60 ml	0.40 ml	0.30 ml	0.20 ml	0.15 ml	0.45 ml	
	0.60 ml	0.40 ml	0.30 ml	0.20 ml	0.50 ml	
		0.50 ml	0.40 ml	0.25 ml		
			0.50 ml			

CUSTOM EXTRACT LABEL OR REMARKS:

THE PRESCRIPTION MUST BE SIGNED BY THE ORDERING PHYSICIAN

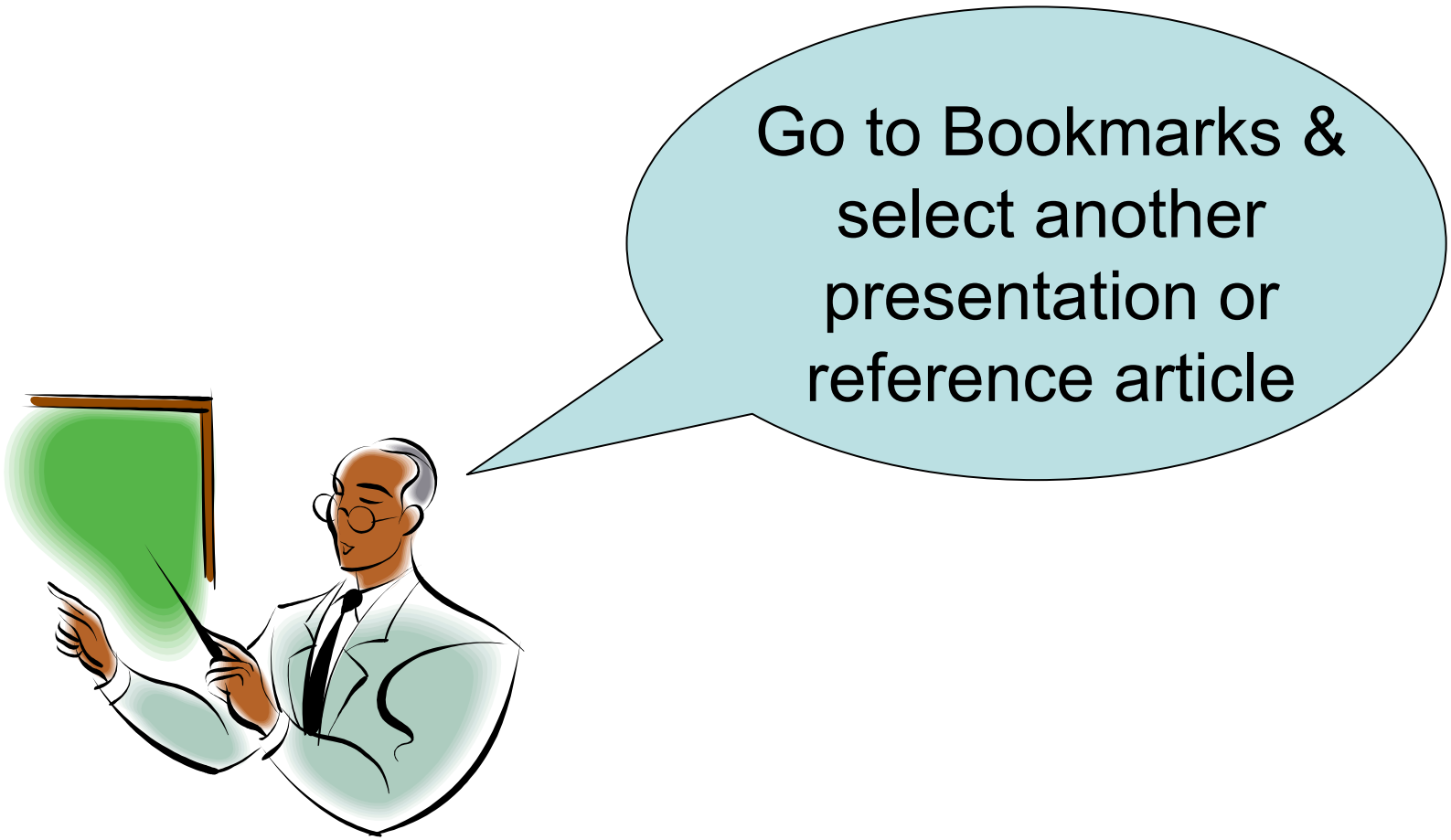
SIGNATURE, RANK, AND DEGREE DATE: January 12, 2007

14A. NAME OF MEDICAL FACILITY
NATIONAL NAVAL MEDICAL CENTER
ALLERGY/IMMUNOLOGY CLINIC
BLDG. 9, 1ST FLOOR
BETHESDA, MD 20853

Capt. J.R. Montgomery MC, USN
Chief, Allergy & Immunology Service

14B. TELEPHONE NUMBER
(301) 295-4510

End of Selection



ALLERGY IMMUNOTHERAPY RECORD NNMC, BETHESDA, MD	SINGLE EXTRACT
Immunotherapy Start Date:	**Immunotherapy Re-evaluation Date:**
RX #	**Extract Contents:** Trees Grasses Weeds Molds
Prior Systemic Allergy Shot Reactions: YES / NO	Roach Dust Mites Cat Dog Other:_____
Peak Flow:	**Peak Flow Parameters**
Beta Blockers: YES / NO	**Consent Signed YES / NO** — **Education Given: YES / NO**

DATE	V/V COLOR	DILUTION	SCD	PEAK FLO	EPI-PEN? Y / N / N/A Health Status: Any Illness? Y / N Any Fever? Y / N	DOSE	TIME	GIVEN BY	VERIF'D BY	ARM (L /R)	RXN-NOW	RXN-DEL	TIME CHKD	CHKD BY

NAME:

RANK:

SSN: **DOB:**

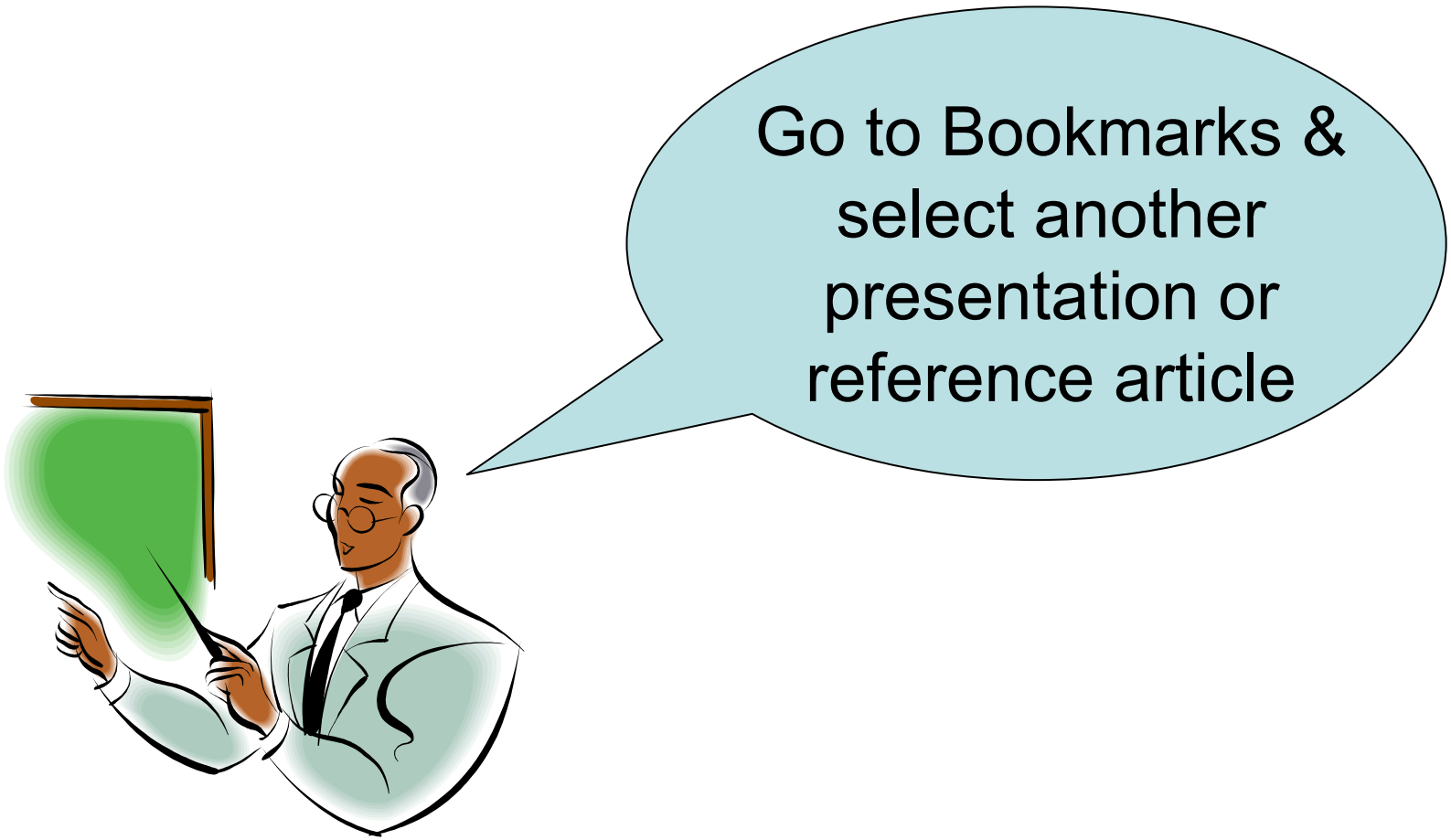
NURSE/TECH/PT'S SIGNATURE & INITIALS

NAME	INITIALS

HYDROCORTISONE/CLOBETASOL: Y / N (CIRCLE WHICH IF YES)
ICE: Y/N ANESTHETIC: Y/N BANDAID: Y/N

Special Instructions

End of Selection



Immunotherapy Pre-Injection Questionnaire

Patient Name:_____
Date:_____

This questionnaire is designed to optimize safety precautions already in place for your allergen immunotherapy injection (s) (allergy shot). Please review and answer the following questions. The nursing staff will review your responses and notify your physician if they have any questions or concerns whether you should receive your injection(s) today.
If you are pregnant or have been diagnosed with a new medical condition, please notify the staff.

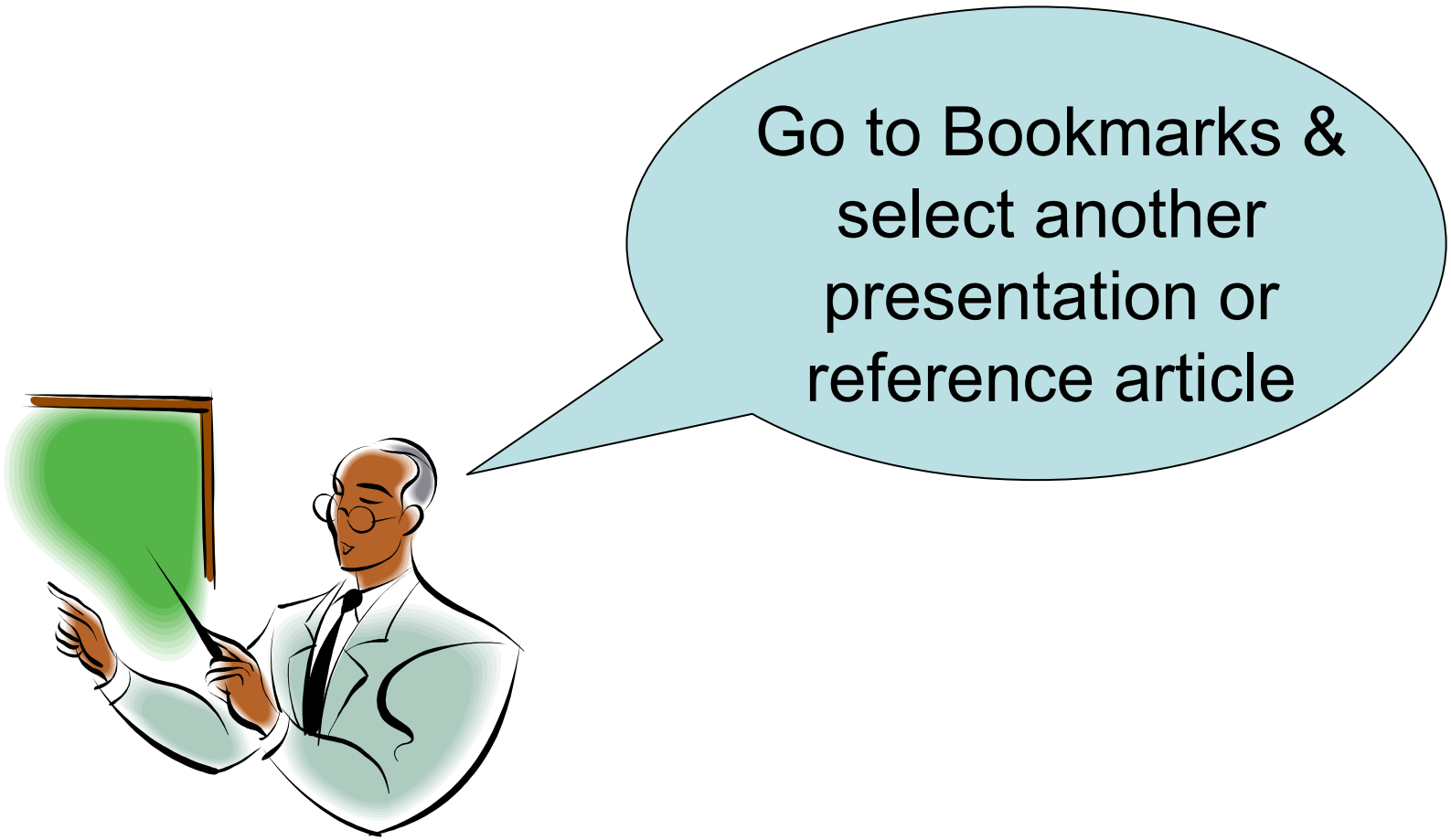
	(Please check appropriate box.)	YES	NO
1.	Have you had increased asthma symptoms (chest tightness, increased cough, wheezing, or felt short of breath) in the past week?		
2.	Have you had increased allergy symptoms (itching eyes or nose, sneezing, runny nose, post-nasal drip, or throat-clearing) in the past week?		
3.	Have you had a cold, respiratory tract infection, or flu-like symptoms in the past two weeks?		
4.	Did you have any problems such as increased allergy or asthma symptoms, hives, or generalized itching within 12 hours of receiving your last injection or swelling that persisted into the next day?		
5.	Are you on any new medications since your last allergy injection? New blood pressure or heart medications, eyedrops, etc.? Please specify:		

Staff intervention/office visit:

_____
_____
_____
_____

Staff Signature: _____

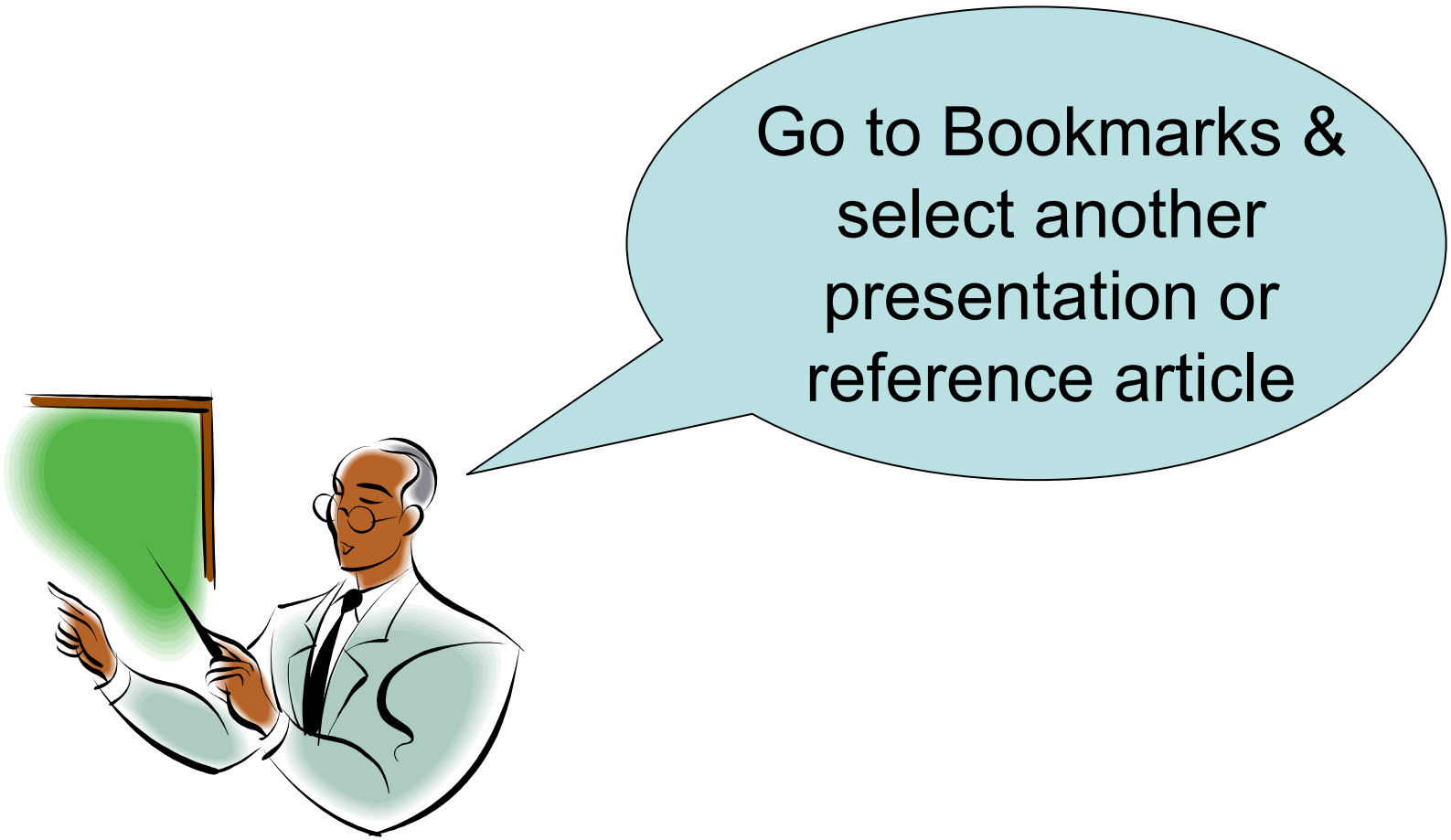
End of Selection



Aeroallergen Dose Adjustment Schedule

Build up phase (1-2/ wk)		
7-13 days late	**Repeat last dose**	**Special Note:** **If 'going back' crosses into the previous vial, go back 1 extra dose**
14-20 days late	**Repeat last dose**	
21-27 days late	**Go back 1 dose from last given**	
28-34 days late	**Go back 2 doses from last given**	
35-41 days late	**Go back 3 doses from last given**	
42-48 days late	**Call office**	
49-55 days late	**Call office**	
> 56 days late	**Call office**	
Maintenance phase (q30 day)		
7-13 days late	**Repeat last dose**	
14-20 days late	**Repeat last dose**	
21-27 days late	**Go back 2 doses from last given**	
28-34 days (1 month) late	**Go back 3 doses from last given**	
35-41 days late	**Go back 4 doses from last given**	
42-55 days late	**Call office**	
> 56 days (2 months) late	**Call office**	
Reaction, local		
< dime size (15mm)	**Advance per schedule**	
nickel size (20mm)	**Advance per schedule**	
quarter size (25mm)	**Go back 1 dose from last given**. Consider split dose, pre-Rx: H1, NSAIDs, etc.	
> quarter size or lasts > 12 hr	**Go back 2 doses from last given**. **Call office if intervention not effective.**	
Reaction, systemic	**Rx emergently. Call office for follow up appointment before resuming protocol.**	

End of Selection



NATIONAL NAVAL MEDICAL CENTER: **Allergy and Immunology**

ON-GOING COMPETENCY ASSESSMENT OF SPECIFIC SKILLS AND PROCEDURES FOR SPECIALTY CARE PATIENTS

Performance Standards: Care of Patients----------Continuum of Care----------Screening----------Assessment----------Education

Demonstrates clinical competency related to specific skills and procedures IAW appropriate standards for care and within defined scope of practice and established guidelines.

CRITICAL BEHAVIOR (SOURCE OF PERFORMANCE STANDARD)	*Self Assess	+Eval Method	Validator's Signature	Day/Month/Year	Comments
1. Patient Screening	**CRITICAL THINKING:** ***Identifies situations where obtaining vital signs is in the best interest of the patient (even if not requested by the provider) and alerts the RN or Health Care Provider (HCP) to the results and the patient's presenting situation. Recognizes abnormal value, takes appropriate action in a timely manner, and documents findings appropriately. Recognizes unique age and language appropriate communication needs of patients and responds appropriately. Recognizes normal variations in vital signs parameters associated with the aging process from toddlers to older adults.***				
A. Obtains VS (pulse, BP, temp, respiration, pulse ox) as requested by the specialty provider and recognizes normal & abnormal values for:					
(1) toddlers (18 months to 3 years)					
(2) preschool age (3-6 years)					
(3) school age (6-10 years)					
(4) adolescents (10-17 years)					
(5) adults (18-64 years)					
(6) geriatric (65 and older)					
B. Obtains weight for allergy and immunology patients and compares to previous visit. Brings significant weight loss/gain to the attention of HCP. (10 pounds change in past 6mos.)					
C. Inquires about presence of pain and uses appropriate pain scales (Wong and Baker FACES Scale, 0-10, etc.) and documents per protocol	**CRITICAL THINKING:** ***Recognizes the influence of age, language, and culture on the perception of pain. Realizes that pain perception often changes with normal aging to include the minimizing normally acute symptoms (i.e., chest pain associated with myocardial infarction or discomforts associated with anaphylactic reactions) in the geriatric population. Inquires as to how the patient manages pain at home (medications, home remedies, restricting activities, etc.) and documents. Alerts nursing staff and/or HCP to presence of pain. .***				
D. Inquires about pertinent safety practices (i.e., inability to perform daily activities due to injuries or disabilities) and alerts RN/HCP for patients who might require additional interventions and documents.					
E. Inquires about increased asthma symptoms, allergy symptoms, respiratory tract symptoms, or any symptom(s) occurring within 12 hrs of previous allergy shot or vaccination.					

***Self Assessment: E = Experienced NP = Needs Practice ND = Never Done NA = Not Applicable (Based on Scope of Practice)**

+Evaluation Method: V = Verbal D = Demonstrated PE = Practical Exercise L = Lecture or Video

I understand that I will be allowed to perform only those tasks listed for my skill level/Scope of Practice, after I have successfully demonstrated competency in those tasks.

Signature: _____Date: _____ Signature of Supervisor: _____ Date: _____

ONGOING COMPETENCY ASSESSMENT OF UNIT SPECIFIC SKILLS & PROCEDURES: Allergy and Immunology

CRITICAL BEHAVIOR (SOURCE OF PERFORMANCE STANDARD)	*Self Assess	+Eval Method	Validator's Signature	Day/Month/Year	Comments
2. Patient Education	**CRITICAL THINKING**: ***Recognizes unique needs of toddlers to geriatric patients and performs procedures accordingly. Gathers age and diagnosis appropriate supplies and equipment. Explains all procedures in an age appropriate manner according to the level of understanding of the patient and family. Approaches patient in non-threatening manner and demonstrates acceptance of their coping mechanisms. Provides teaching and reassurance throughout the entire process.***				
A. Greets patient/family and establishes a rapport.					
B. Screens for learning needs, barriers to learning and preferred learning method(s).					
C. Provide information to meet educational needs or refers to appropriate resources (i.e. VIS, handouts, immunotherapy-specific patient education class, Nurse Educator or HCP)					
D. Documents education provided on progress note, order form, screening questionnaire or electronically.					
(1) Toddlers (18 months-3 years)	**CRITICAL THINKING FOR TODDLERS:** ***Encourages parent to provide child with a security item (blanket, toy) and have parent stay with child. Gives toddler one step directions at their eye level and maintains eye contact during examination. Speaks in slow and calm manner and praises toddler at completion of examination.***				
(2) Pre-School age (3-6 years)	**CRITICAL THINKING FOR PRE-SCHOOL AGE:** ***Involves child and parent in all decisions and encourages child to participate in examination as much as possible (i.e., handling equipment to reduce fear and satisfy curiosity).Provides a safe environment, explains all steps using simple words the child can understand, and uses distraction technique such as songs or asking questions about favorite activities or pets. Provides for minimal exposure due to particular modesty of this age group. Praises child at the completion of the examination.***				
(3) School age (6-10 years)	**CRITICAL THINKING FOR SCHOOL AGE:** ***Involves child and parent in all decisions and encourages child to participate in n examination as much as possible. Provides a safe environment and maintains modesty. Allows child to choose whether parent remains present if appropriate. Praises child at the completion of the examination.***				
(4) Adolescents (10-17 years)	**CRITICAL THINKING FOR ADOLESCENTS:** ***Involves adolescent and parent in all decisions and encourages the adolescent to participate in examination as much as possible. Supplements explanations with rationale. Provides a safe environment and maintains modesty. Allows adolescent to choose whether parent remains present if appropriate. Encourages adolescent to ask questions and express concerns/fears regarding illness. Talks directly to the adolescent and allows them to answer questions even if a parent is present. Does not treat adolescent like a child.***				
(5) Adults (18-64 years)	**CRITICAL THINKING FOR ADULTS (18-64):** ***Addresses patient by name and/or rank per their preference. Explains examinations/ procedures in clear and simple terms using correct terminology. Maintains safety and provides reassurance.***				
(6) Geriatric (64 plus)	**CRITICAL THINKING FOR OLDER ADULTS:** ***Shows respect for patient and family and addresses patient by name and/or rank per their preference avoiding such terms as "honey, sweetie, or cutie". Involves patient and family in all decisions and encourages the patient to participate in procedure as much as possible. Recognizes that older patients may demonstrate a delayed response to questions and allows them time to phrase an answer. Also adjusts explanations to accommodate short-term memory loss. Explains examinations/procedures in clear and simple terms using correct terminology. Allows patient to describe their mobility capabilities and limitations in regard to positioning. Maintains safety and provides reassurance. Minimizes exposure to ensure modesty and avoid unnecessary heat loss.***				

Name: _____

***Self Assessment: E = Experienced NP = Needs Practice ND = Never Done NA = Not Applicable (Based on Scope of Practice)**

+Evaluation Method: V = Verbal D = Demonstrated PE = Practical Exercise L = Lecture or Video

ONGOING COMPETENCY ASSESSMENT OF UNIT SPECIFIC SKILLS & PROCEDURES: Allergy and Immunology

CRITICAL BEHAVIOR (SOURCE OF PERFORMANCE STANDARD)	*Self Assess	+Eval Method	Validator's Signature	Day/Month/Year	Comments
3. Patient Care: **IMMUNOTHERAPY/IMMUNIZATIONS**	**CRITICAL THINKING**: ***Recognizes unique needs of toddlers through geriatric patients and performs examinations/procedures accordingly. Gathers age and diagnosis appropriate supplies and equipment. Explains all examinations/procedures in an age appropriate manner according to the level of understanding of the patient and the family. Approaches patient in professional and non-threatening manner. Serves as a chaperone for physical exams as needed. Provides reassurance to patient and family.***				
A. Assures a physician order is available prior to administering immunotherapy/immunizations.					
B. Screens patient's records for required immunotherapy/ immunization(s).					
C. Documents date, vial/lot number, amount, manufacturer and site of vaccine to be given as appropriate for vaccination.					
D. Measures pulmonary function IAW clinic policy.					
E. Assures educational needs are met IAW clinic policy.					
F. Obtains appropriate vaccine(s) and gathers supplies for administration.	**CRITICAL THINKING:** *Recognizes appropriate size needle gauge and length based on patient's age and size considering the route of administration.*				
G. Checks expiration date on vaccines and diluents.					
H. Dilutes appropriately and draws up right vaccine and dose.					
I. Explains the procedure to patient.					
J. Reviews and clarifies screening questions (immunodeficiency, allergies, pregnancy, worsening symptoms, new medications).					
K. Appropriately refers to HCP, if needed.					
L. Washes or sanitizes hands between patient contacts and uses proper aseptic technique.					
M. Carefully check and administer vaccine(s) utilizing the five (5) rights to giving medications.	**CRITICAL THINKING**: ***Focus on the right medication (age specific vaccine, IT prescription#, allergen contents, concentration), right dose (age/dose specific, VIT vs AIT), via the right route to the right patient at the right time interval.***				
N. Cleanses the site "center to outward", approximately 2" around it. Allows the site to dry.					
O. Inserts the needle at the correct angle to the skin for SC or for IM as appropriate to the immunotherapy/vaccine.					
P. Aspirates prior to injecting vaccine.					
Q. Applies gentle pressure to injection site for several seconds after each injection. Does NOT rub immunotherapy site.					
R. Properly disposes of needle, syringe and empty vials in sharps container.					

Name: _____

***Self Assessment: E = Experienced NP = Needs Practice ND = Never Done NA = Not Applicable (Based on Scope of Practice)**

+Evaluation Method: V = Verbal D = Demonstrated PE = Practical Exercise L = Lecture or Video

ONGOING COMPETENCY ASSESSMENT OF UNIT SPECIFIC SKILLS & PROCEDURES: Allergy and Immunology

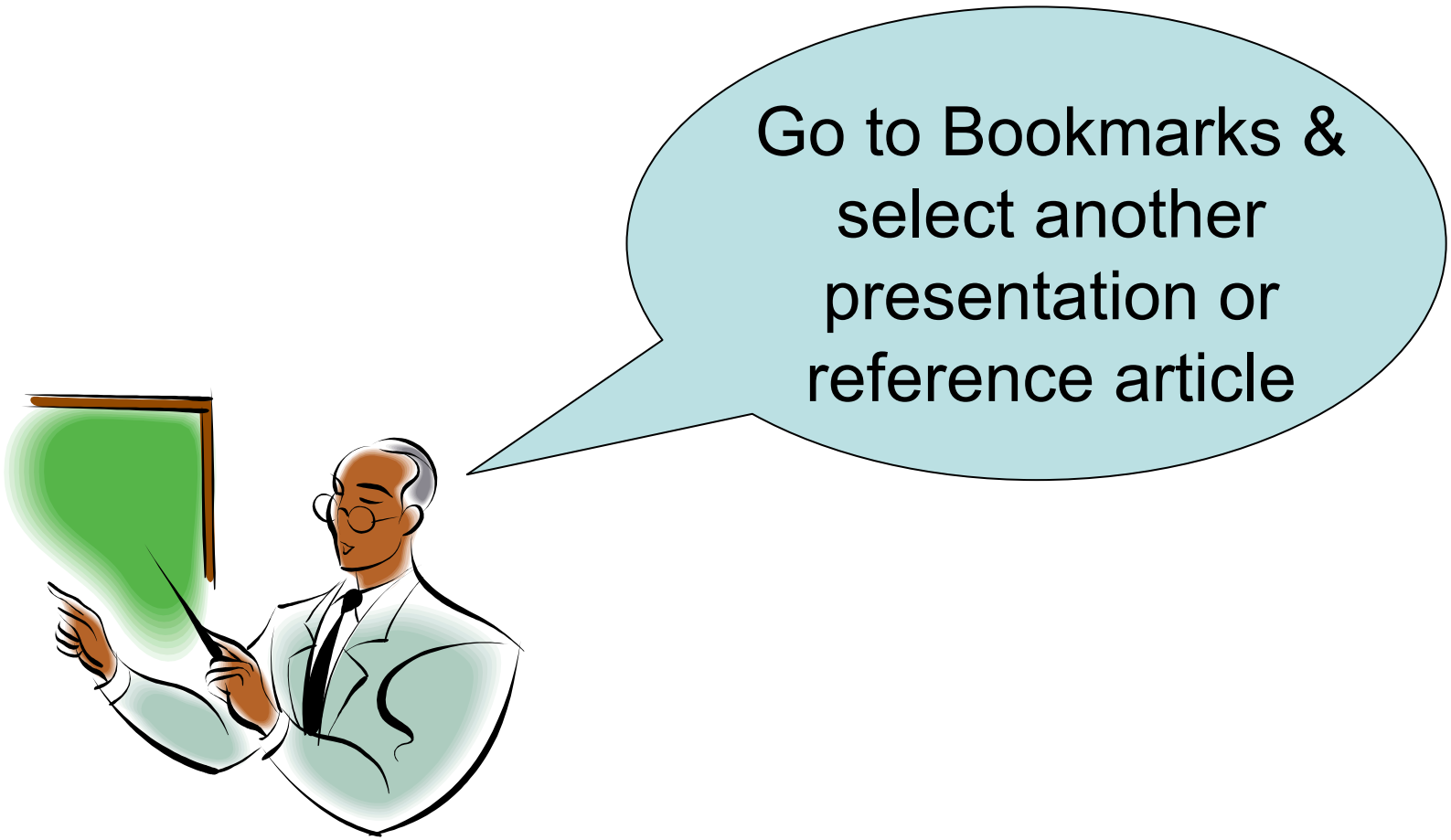
CRITICAL BEHAVIOR (SOURCE OF PERFORMANCE STANDARD)	*Self Assess	+Eval Method	Validator's Signature	Day/Month/Year	Comments
S. Explains some post injection comfort measures and instructs the patient to wait in the clinic lobby for 30 minutes for JEV and immunotherapy injections, and 15 minutes for all other vaccines.					
T. Advises the patient to contact any nurse, technician, or doctor in the clinic if they began to feel "different" than prior to shot.					
U. Documents local reaction at site of injection prior to departing the clinic and any delayed reaction prior to administering next shot.					
ADVERSE REACTIONS	**CRITICAL THINKING: *Understands the purpose of the medication and its intended effect. Recognizes systemic reactions to vaccines. (Anaphylaxis vs vasovagal)***				
A. Recognizes adverse systemic reactions	**CRITICAL THINKING: *Patients with post-shot vasovagal reactions tend to be lightheaded, pale, and have slower pulses, while patients suffering post-shot allergic anaphylaxis tend to be flushed and tachycardic, and may have hives, shortness of breath, cough, wheeze, and/or GI cramping.***				
B. Calls for Help					
C. Positions patient (supine, Trendelenburg)					
D. Administers age-appropriate dose of epinephrine IM					
(1) Less than 60 pounds = 0.15 cc of 1:1,000 Epinephrine					
(2) Greater than 60 pounds = 0.30 cc of 1:1,000 Epinephrine					
E. Assesses ABC's and continually monitors vital signs					
F. Administers Oxygen					
G. Appropriately annotates medical record					
H. Arranges follow up appointment with Allergist.					
I. Provides patient with epinephrine autoinjector					
(1) Instructs patient/parent in indication(s) for use					
(2) Instructs patient/parent in correct technique for use					
(3) Monitors for compliance					

Name: _____

***Self Assessment: E = Experienced NP = Needs Practice ND = Never Done NA = Not Applicable (Based on Scope of Practice)**

+Evaluation Method: V = Verbal D = Demonstrated PE = Practical Exercise L = Lecture or Video

End of Selection



Allergy immunotherapy administration by licensed nursing staff

By Arline M. Gerard, RN, Kaiser Orange County, CA

It is within the scope of practice of licensed nurses to administer allergy immunotherapy medications for the purpose of treatment of allergy patients.

Authority for nurses to administer medications derives from varying sections of their states' Nurse Practice Act (NPA). Most states place few limits on the type of medication or route of administration; there is often only a requirement that the drug be ordered by one lawfully authorized to prescribe it. Other relevant sections of some NPA's do impose additional requirements, but these generally do not pertain to allergy immunotherapy extract vaccines. Specifically, the nurse should be competent to perform the function of administering medications, and this task must be performed in a manner consistent with the standard of practice expected of a diligent nurse, in that state.

In administering medication/extracts for treatment of allergy patients, the nurse is required to have the same knowledge and skills as for any other medication that she/he administers. This knowledge base includes, but is not limited to:

- Effects of the medication/extract
- Potential side effects of the medication/extract
- Contraindications for the administration of the medication/extract
- Amount of the medication/extract to be administered
- Dilution of the medication/extract to be administered

The requisite skills include the ability to competently and safely administer the medication/extract by the specified route, anticipate and recognize potential complications of the medication/extract, recognize emergency situations, and institute emergency procedures. Thus, the nurse would be held accountable for knowledge of the medication/extract and for ensuring that the proper safety measures are followed.

As of March 2003, safety considerations for allergy immunotherapy administration include the standards embodied in the Practice Parameters. These national standards were issued jointly by the American Academy of Allergy, Asthma & Immunology with the American College of Allergy, Asthma & Immunology. The Practice Parameters should be consulted in establishing and maintaining allergy office policies and procedures.

The nurse administering allergy immunotherapy should conduct a brief nursing assessment to determine that administration of the medication/extract is in the patient's best interest, for that visit. The nurse would also ensure that all safety measures are enforced, including back-up personnel skilled and trained in airway management, resuscitation and emergency intubation, should complications occur. Nurses managing the care of patients receiving allergy immunotherapy shall expect the patient to wait, post injection. The nurse should not engage in tasks that would seriously compromise monitoring of the patient by the nurse. The nurse must have knowledge of signs and symptoms of a reaction to the medication/extract, and must be empowered to give epinephrine and other treatments, immediately, when determined to be necessary.

A nurse is held accountable for any act of nursing provided to a patient. The nurse has the right and obligation to act as the patient's advocate by refusing to administer or continue to administer any medication/extract not in the patient's best interest; this includes medication/extracts which may cause the patient to have an anaphylactic event, especially when given in error. Basic immunotherapy forms

reflecting current robust documentation standards, as well as office policy and procedure manuals should be reviewed and updated at reasonable intervals.

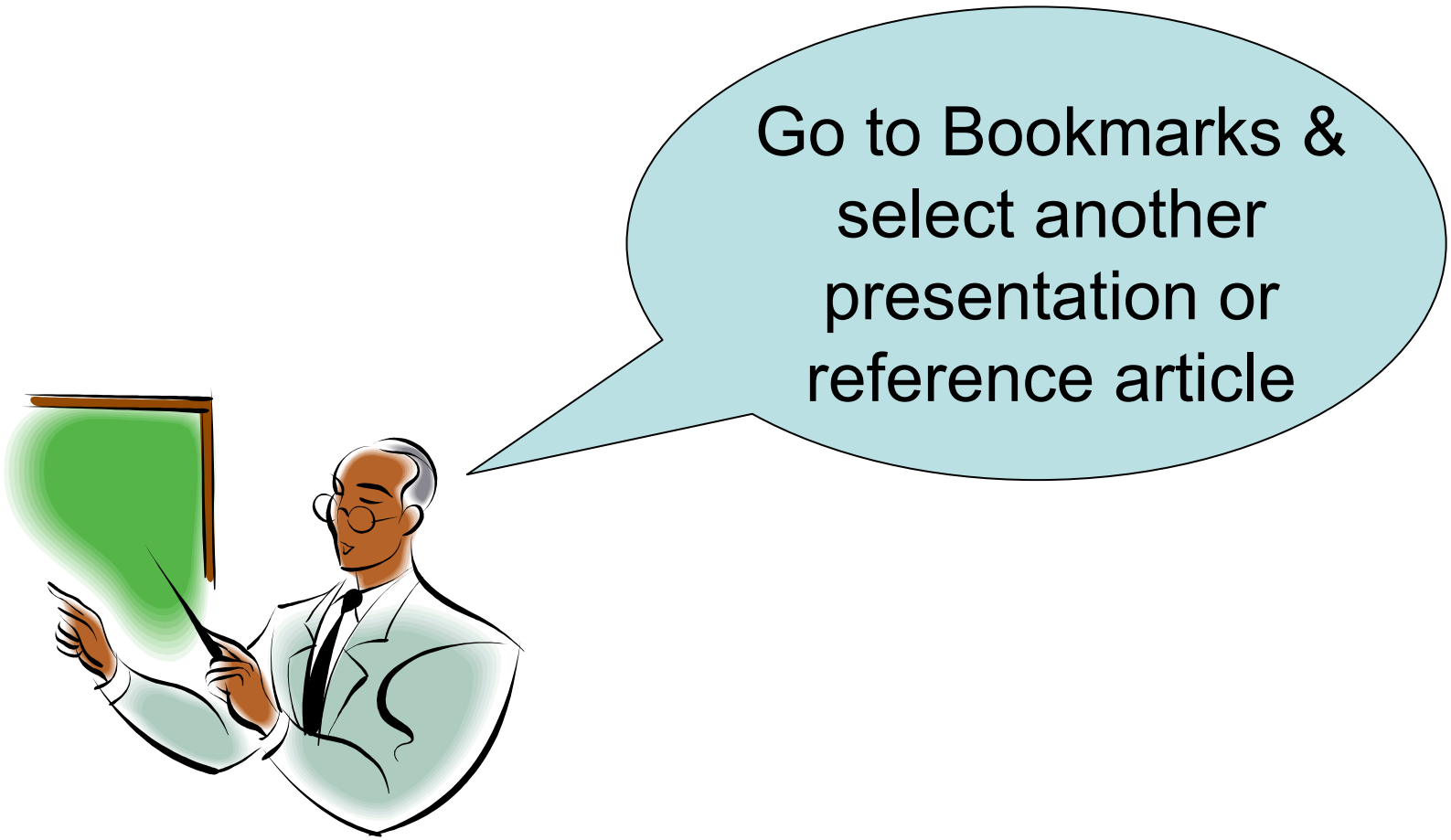
All nursing and support staff should have in-services to reflect knowledge changes, as the profession of the allergy nurse evolves. As offices transition to computerized systems, the nurse is still responsible for the actual administration of the medication/extract, and should be engaged in finding and reducing errors, and potential errors which may be inherent within their computerized programming. He/she should never knowingly give a medication/extract which he/she reasonably deems to be improper, for that patient.

The institution or employer should have in place a process for evaluating and documenting the nurse's demonstration of the knowledge, skills, and abilities for management of patients receiving allergy immunotherapy. Evaluation and documentation of these competency skills should occur on a regular basis.

Immediate availability of epinephrine and of an emergency cart, which contains resuscitative and antagonist medications, airway and ventilator adjunct equipment, defibrillator, suction, and a source for administration of oxygen are commonly included in current standards for giving allergy immunotherapy.

Registered nurse practitioners, by virtue of advanced education and practice in their area of allergy specialty, may, or should have met, these requirements to safely administer allergy immunotherapy, but only if properly trained to do so.

End of Selection



Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
Co-editors: **James T. Li, MD, Harold Nelson, MD, and Richard Lockey, MD**

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second update." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

Published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

Disclosure of potential conflict of interest: L. Cox has consulting arrangements with Allergy Therapeutics, Genentech/Novartis, and Greer Laboratories and is on the speakers' bureau for Genentech/Novartis, GlaxoSmithKline, and AstraZeneca. R. Lockey has received grant support from Greer Laboratories; served as chairman of an advisory committee for ALK-Abelló for over 7 years; and has served as an expert witness for allergen immunotherapy death for both plaintiff and defendant. H. Nelson has consulting arrangements with Genentech/Novartis, Curalogic, GlaxoSmithKline, Inflazyme Pharmaceuticals, Dey Laboratories, Dynavax Technologies, Altana, and Schering-Plough; has received grant support from Dey Laboratories, IVAX, MediciNova, Wyeth, Sepracor, Genentech, Schering-Plough, Novartis, AstraZeneca, SkyPharma, Altana, and Roche; and is on the speakers' bureau for GlaxoSmithKline and AstraZeneca. D. Bernstein has consulting arrangements with ALK-Abelló and has received grant support from Dynavax and ALK-Abelló. J. Blessing-Moore has received grant support from Novartis-Genentech and AstraZeneca and is on the speakers' bureau for Schering-Plough, Merck, Aventis, Novartis/Genentech, AstraZeneca. D. M. Lang has consulting arrangements with, has received grant support from, and is on the speakers' bureau for GlaxoSmithKline, Merck, AstraZeneca, Centocor, Sanofi-Aventis, Schering-Plough, Verus, and Dey. J. Oppenheimer has consulting arrangements with GlaxoSmithKline, AstraZeneca, Sepracor, and Merck; has received grant support from AstraZeneca, Sepracor, and Merck, Boehringer Ingelheim, Novartis/Genentech, and Schering-Plough; and is on the speakers' bureau for GlaxoSmithKline, AstraZeneca, Sepracor, and Merck. J. M. Portnoy has consulting arrangements with Greer and GlaxoSmithKline; has received grant support from Clorox; and is on the speakers' bureau for Schering-Plough, Merck, Aventis, Secpracor, and AstraZeneca. S. A. Tilles has consulting arrangements with Genentech, Schering-Plough, and GlaxoSmithKline; has received grant support from AstraZeneca, Novartis, Medpoint, Apieron, and ALK-Abelló; and is on the speakers' bureau for GlaxoSmithKline, Pfizer, Genentech, and Alcon. The rest of the authors have declared that they have no conflict of interest.

Reprint requests: Joint Council of Allergy, Asthma and Immunology, 50 N Brockway St, #3-3, Palatine, IL 60067.

J Allergy Clin Immunol 2007;120:S25-85.
0091-6749/$32.00

doi:10.1016/j.jaci.2007.06.019

18. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy 2005; 94(suppl):S1-S63.
19. Attaining optimal asthma control: a practice parameter. J Allergy Clin Immunol 2005;116(suppl):S3-S11.
20. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol 2005; 116(suppl):S13-S47.
21. Food allergy: a practice parameter. Ann Allergy Asthma Immunol 2006;96(suppl 2):S1-S68.
22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

These parameters are also available on the internet at http://www.jcaai.org.

CONTRIBUTORS

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

The Joint Task Force gratefully acknowledges the American Academy of Allergy, Asthma and Immunology Board of Directors and the American College of Allergy, Asthma and Immunology Board of Regents for their review and support of this document.

SUPPLEMENT EDITOR

Linda Cox, MD
Department of Medicine
Nova Southeastern University College of Osteopathic Medicine
Davie, Fla

CO-EDITORS

James T. Li, MD, PhD
Division of Allergic Diseases
Mayo Clinic
Rochester, Minn
Richard Lockey, MD
Departments of Medicine, Pediatrics, and Public Health
Division of Allergy and Immunology
University of South Florida College of Medicine
James A. Haley Veterans' Hospital
Tampa, Fla
Harold Nelson, MD
Department of Medicine
National Jewish Medical and Research Center
Denver, Colo

JOINT TASK FORCE REVIEWERS

David Bernstein, MD
Department of Medicine and Environmental Health
University of Cincinnati College of Medicine
Cincinnati, Ohio
I. Leonard Bernstein, MD
Departments of Medicine and Environmental Health
University of Cincinnati College of Medicine
Cincinnati, Ohio
David A. Khan, MD
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Tex
Joann Blessing-Moore, MD
Departments of Medicine and Pediatrics
Stanford University Medical Center
Department of Immunology
Palo Alto, Calif
David M. Lang, MD
Allergy/Immunology Section
Division of Medicine
Allergy and Immunology Fellowship Training Program
Cleveland Clinic Foundation
Cleveland, Ohio
Richard A. Nicklas, MD
Department of Medicine
George Washington Medical Center
Washington, DC
John Oppenheimer, MD
Department of Internal Medicine
New Jersey Medical School
Pulmonary and Allergy Associates
Morristown, NJ
Jay M. Portnoy, MD
Section of Allergy, Asthma & Immunology
The Children's Mercy Hospital
Department of Pediatrics
University of Missouri-Kansas City School of Medicine
Kansas City, Mo
Diane E. Schuller, MD
Department of Pediatrics
Pennsylvania State University Milton S. Hershey Medical College
Hershey, Pa
Sheldon L. Spector, MD
Department of Medicine
UCLA School of Medicine
Los Angeles, Calif
Stephen A. Tilles, MD
Department of Medicine
University of Washington School of Medicine
Redmond, Wash
Dana V. Wallace, MD
Nova Southeastern University
Davie, Fla

INVITED REVIEWERS

Don Aaronson, MD, Chicago, Ill
David Golden, MD, Baltimore, Md
Moises Calderon, MD, London, United Kingdom (UK)

Stephen Durham, MD, London, UK
Ira Finegold, MD, New York, NY
Stephen Kemp, Jackson, Miss
Brian Smart, MD, Glen Ellyn, Ill
Mark L. Vandewalker, MD, Columbia, Mo
Richard Weber, MD, Denver, Colo
David Weldon, MD, College Station, Tex

REVIEWERS OF ALLERGEN EXTRACT SECTION

Robert Esch, PhD, Lenoir, NC
Larry Garner, CPT, BA, Spokane, Wash
Richard Lankow, PhD, Round Rock, Tex
Greg Plunkett, PhD, Round Rock, Tex
Tom Willoughby, Liberty, Miss
The authors and editors gratefully acknowledge Susan Grupe for her administrative assistance.

Allergen immunotherapy: A practice parameter second update

PREFACE

This document was developed by the Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma and Immunology (AAAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI).

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. This parameter is intended to establish guidelines for the safe and effective use of allergen immunotherapy, while reducing unnecessary variation in immunotherapy practice. These guidelines have undergone an extensive peer-review process consistent with recommendations of the American College of Medical Quality's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation (Table I).[3] Laboratory-based studies were not rated.

The working draft of ''Allergen immunotherapy: a practice parameter second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. The authors carefully considered all of these comments in preparing the final version. An annotated algorithm in this document summarizes the key decision points for the appropriate use of allergen immunotherapy (Fig 1).

The section on efficacy summarizes the evidence demonstrating that allergen immunotherapy is effective in the management of properly selected patients with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of systemic reactions.

Specific recommendations guide the physician in selecting those patients for whom allergen immunotherapy is appropriate. Aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

TABLE I. Classification of evidence and recommendations*

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least 1 randomized controlled trial
IIa	Evidence from at least 1 controlled study without randomization
IIb	Evidence from at least 1 other type of quasiexperimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions, clinical experience of respected authorities, or both
LB	Evidence from laboratory-based studies
NR	Not rated
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II, or III evidence
NR	Not rated

*Adapted with permission from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.[3]

The selection of allergens for immunotherapy is based on clinical history, the presence of specific IgE antibodies, and allergen exposure. This parameter offers suggestions and recommendations derived from known patterns of allergen cross-reactivity. Recognizing that the immunotherapy terminology used to describe extract dilutions is sometimes ambiguous, the 2003 ''Allergen immunotherapy: a practice parameter'' established standardized terminology for describing allergen immunotherapy extract dilutions. These parameters also provided specific recommendations for immunotherapy maintenance doses for some standardized allergens and a suggested dosing range for nonstandardized allergen extracts. The therapeutic preparations for allergen immunotherapy are extracted from source materials, such as pollen, mold cultures, and pelt, hence the traditional term *allergen extract*. The terms *allergen extract* or *extract* refer to solutions of proteins or glycoproteins extracted from source material not yet incorporated into a therapeutic allergen immunotherapy extract. The term *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. All dilutions should be referenced to the maintenance concentrate and should be noted as a volume-to-volume dilution (eg, 1:100 vol/vol dilution of a maintenance concentrate).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

This document was approved by the sponsoring organizations and represents an evidence-based, broadly accepted consensus opinion. These clinical guidelines are designed to assist clinicians by providing a framework for the evaluation and treatment of patients and are not intended to replace a clinician's judgment or establish a protocol for all patients. Not all recommendations will be appropriate for all patients. Because this document incorporates the efforts of many participants, no individual, including anyone who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these guidelines. Recognizing the dynamic nature of clinical practice and practice parameters, the recommendations in this document should be considered applicable for 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

ALGORITHM AND ANNOTATIONS FOR IMMUNOTHERAPY

Fig 1 provides an algorithm for the appropriate use of allergen immunotherapy. Given below are annotations for use with the algorithm.

Box 1

Immunotherapy is effective in the management of allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity. Allergen immunotherapy

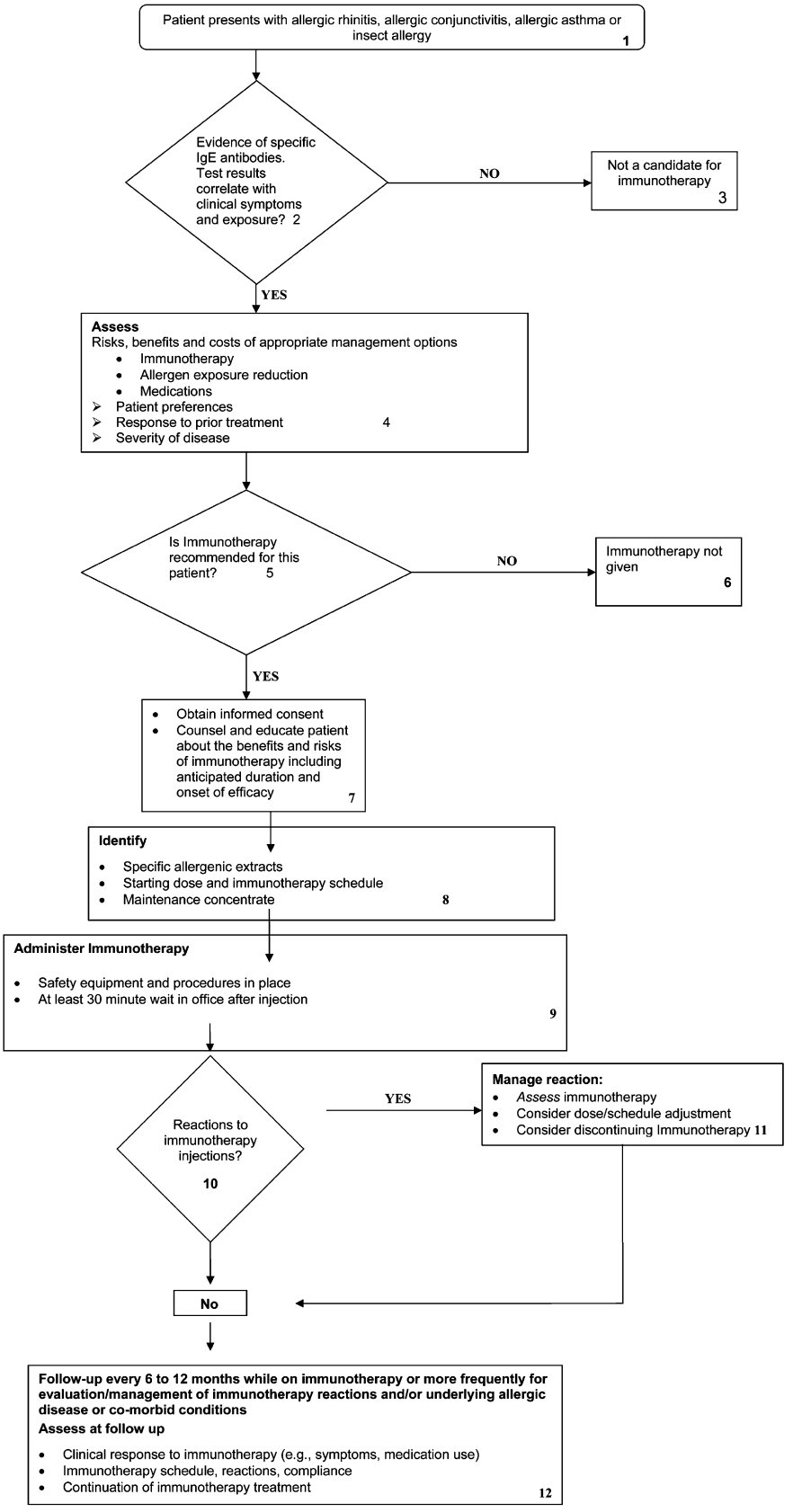


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for specific IgE antibodies is useful under certain circumstances. Immunotherapy should be considered when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure.

Box 3

Immunotherapy should not be given to patients with negative test results for specific IgE antibodies or those with positive test results for specific IgE antibodies that do not correlate with suspected triggers, clinical symptoms, or exposure. This means that the presence of specific IgE antibodies alone does not necessarily indicate clinical sensitivity. There is no evidence from well-designed studies that immunotherapy for any allergen is effective in the absence of specific IgE antibodies.

Box 4

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management options. Each of the 3 major management approaches (allergen immunotherapy, allergen exposure reduction, and pharmacotherapy) has benefits, risks, and costs. Furthermore, the management plan must be individualized, with careful consideration given to patient preference. Disease severity and response (or lack of response) to previous treatment are important factors.

Box 5

The physician and patient should discuss the benefits, risks, and costs of the appropriate management options and agree on a management plan. On the basis of clinical considerations and patient preference, allergen immunotherapy might or might not be recommended. Patients with allergic rhinitis/conjunctivitis or allergic asthma whose symptoms are not well controlled by medications or avoidance measures or require high medication doses, multiple medications, or both to maintain control of their allergic disease might be good candidates for immunotherapy. Patients who experience adverse effects of medications or who wish to avoid or reduce the long-term use of medications are good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

Box 6

After careful consideration of appropriate management options, the physician and patient might decide not to proceed with immunotherapy.

Box 7

Before immunotherapy is started, patients should understand its benefits, risks, and costs. Counseling should also include the expected onset of efficacy and duration of treatment, as well as the risk of anaphylaxis and importance of adhering to the immunotherapy schedule.

Box 8

The physician prescribing immunotherapy should be trained and experienced in prescribing and administering immunotherapy. The prescribing physician must select the appropriate allergen extracts on the basis of that particular patient's clinical history and allergen exposure history and the results of tests for specific IgE antibodies. The quality of the allergen extracts available is an important consideration. When preparing mixtures of allergen extracts, the prescribing physician must take into account the cross-reactivity of allergen extracts and the potential for allergen degradation caused by proteolytic enzymes. The prescribing physician must specify the starting immunotherapy dose, the target maintenance dose, and the immunotherapy schedule (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) for standardized allergen extracts. For nonstandardized extracts, a suggested maintenance dose is 3000 to 5000 protein nitrogen units (PNU) or 0.5 mL of a 1:100 wt/vol dilution of manufacturer's extract. If the major allergen concentration of the extract is known, a range between 5 and 20 μg of major allergen is the recommended maintenance dose for inhalant allergens and 100 μg for Hymenoptera venom. Immunotherapy treatment can be divided into 2 periods, which are commonly referred to as the *build-up* and *maintenance phases*.

The immunotherapy build-up schedule (also referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 to 28 weeks. In conventional schedules a single dose increase is given on each visit, and the visit frequency can vary from 1 to 3 times a week. Accelerated schedules, such as rush or cluster immunotherapy, entail administration of several injections at increasing doses on a single visit. Accelerated schedules offer the advantage of achieving the therapeutic dose earlier but might be associated with increased risk of systemic reaction in some patients.

Box 9

Immunotherapy should be administered in a setting that permits the prompt recognition and management of adverse reactions. The preferred location for such administration is the prescribing physician's office. However, patients can receive immunotherapy injections at another health care facility if the physician and staff at that location are trained and equipped to recognize and manage immunotherapy reactions, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring peak expiratory flow rate before administering an immunotherapy injection and withholding an immunotherapy injection if the peak expiratory flow rate is considered low for that patient. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

Box 11

Local reactions can be managed with local treatment (eg, cool compresses or topical corticosteroids) or antihistamines. Systemic reactions can be mild or severe (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

Antihistamines and systemic corticosteroids are secondary medications that might help to modify systemic reactions but should never replace epinephrine in the treatment of anaphylaxis. Intravenous saline or supplemental oxygen might be required in severe cases. For additional details, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

Box 12

Patients receiving maintenance immunotherapy should have follow-up visits at least every 6 to 12 months. Periodic visits should include a reassessment of symptoms and medication use, the medical history since the previous visit, and an evaluation of the clinical response to immunotherapy. The immunotherapy schedule and doses, reaction history, and patient compliance should also be evaluated. The physician can at this time make adjustments to the immunotherapy schedule or dose, as clinically indicated.

There are no specific markers that will predict who will remain in clinical remission after discontinuing effective allergen immunotherapy. Some patients might sustain lasting remission of their allergic symptoms after discontinuing allergen immunotherapy,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] As with the decision to initiate allergen immunotherapy, the decision to discontinue treatment should be individualized, taking into account factors such as the severity of the patient's illness before treatment, the treatment benefit sustained, and the inconvenience immunotherapy represents to a specific patient and the potential effect a clinical relapse might have on the patient. Ultimately, the duration of immunotherapy should be individualized on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

The *allergen immunotherapy extract* is defined as the mixture of the manufacturer's allergen extract or extracts that is used for allergen immunotherapy. Allergen extracts used to prepare the allergen immunotherapy extract can be complex mixtures containing multiple allergenic and nonallergenic macromolecules (proteins, glycoproteins, and polysaccharides) and low-molecular-weight compounds (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] and *allergen solution*.

Allergen immunotherapy is defined as the repeated administration of specific allergens to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

Anaphylaxis is an immediate systemic reaction often occurring within minutes and occasionally as long as an hour or longer after exposure to an allergen. It can be IgE mediated, as can occur with allergen immunotherapy, or non–IgE mediated, as occurs with radiocontrast media. It is caused by the rapid release of vasoactive mediators from tissue mast cells and peripheral blood basophils.

The *build-up phase* involves receiving injections with increasing amounts of the allergen. The frequency of

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

injections during this phase generally ranges from 1 to 3 times a week, although more rapid build-up schedules are sometimes used. The duration of this phase depends on the frequency of the injections but generally ranges from 3 to 6 months (at a frequency of 2 times and 1 time per week, respectively).

Cluster immunotherapy is an accelerated build-up schedule that entails administering several injections at increasing doses (generally 2-3 per visit) sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is generally achieved more rapidly than with a conventional (single injection per visit) build-up schedule (generally within 4 to 8 weeks).

Desensitization is the rapid administration of incremental doses of allergens or medications by which effector cells are rendered less reactive or nonreactive to an IgE-medicated immune response. Desensitization can involve IgE-mediated or other immune mechanisms. The positive skin test response to the allergens might diminish or actually convert to a negative response in some cases after this procedure. Tolerance to medications can be achieved through desensitization.

The *dose* is the actual amount of allergen administered in the injection. The volume and concentration can vary such that the same delivered dose can be given by changing the volume and concentration (ie, 0.05 mL of a 1:1 vol/vol allergen would equal 0.5 mL of a 1:10 vol/vol allergen). The dose can be calculated by using the following formula: concentration of allergen multiplied by volume of administered dose (see Table II for a dose-calculation table).

The *effective therapeutic dose* or *maintenance dose* is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions. The effective therapeutic dose might not be the initially calculated *projected effective* dose (eg, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

Hyposensitization is a term formerly used interchangeably with *allergen immunotherapy*. It was introduced to distinguish allergen immunotherapy from classical desensitization. Hyposensitization denotes a state of incomplete desensitization because complete desensitization is rarely accomplished with allergen immunotherapy.

Immunomodulation is a term that denotes a wide variety of drug or immunologic interventions that alter normal or abnormal immune responses by deletion of specific T cells, B cells, or both; immune deviation; induction of peripheral/central tolerance; or modification of various inflammatory pathways (eg, chemotaxis, adhesions, or intracytoplasmic signaling).

Immunotherapy is a treatment modality that appeared soon after adaptive immune responses were discovered and has gradually evolved to encompass any intervention that might benefit immune-induced aberrant conditions by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving a host's defenses against microorganisms. Allergen immunotherapy was originally conceived as a form of active immunization, the purpose of which was to alter the host's abnormal immune responses and not augment the host's defenses against microorganisms. The modern rubric of immunotherapy includes all methods used to overcome abnormal immune responses by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual or mixtures of manufacturer's allergen extracts intended for allergen immunotherapy treatment. A maintenance concentrate can be composed of a concentrated dose of a single allergen or a combination of concentrated allergens to prepare an individual patient's customized allergen immunotherapy extract mixture. Subsequent dilutions can be prepared from the

maintenance concentrate for the build-up phase or if the patient cannot tolerate the maintenance concentrate.

The *maintenance dose* (or *effective therapeutic dose*) is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions. The effective therapeutic dose may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. Not all patients will tolerate the projected effective dose, and some patients experience therapeutic efficacy at lower doses.

The *maintenance phase* begins when the effective therapeutic dose is reached. Once the maintenance dose is reached, the intervals between the allergy injections are increased. The dose generally is the same with each injection, although modifications can be made based on several variables (ie, new vials or a persistent large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges from 4 to 8 weeks for venom and every 2 to 4 weeks for inhalant allergens but can be advanced as tolerated if clinical efficacy is maintained.

A *major allergen* is an antigen that binds to the IgE sera from 50% or more of a clinically allergic group of patients. Such allergens are defined either by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see maintenance goal.

Rush immunotherapy is an accelerated immunotherapy build-up schedule that entails administering incremental doses of allergen at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved. Rush immunotherapy schedules for inhalant allergens can be associated with a greater risk of systemic reactions, particularly in high-risk patients (eg, those with markedly positive prick/puncture test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic antisera by Jenner, Pasteur, Koch, and von Behring, were effective for disease prevention. These initial efforts in immune modulation served as a model for later developments in the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] Advances in allergen immunotherapy have depended on the improved understanding of IgE-mediated immunologic mechanisms, the characterization of specific antigens and allergens, and the standardization of allergen extracts. Proof of the efficacy of allergen immunotherapy has accumulated rapidly during the past 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

Effective subcutaneous allergen immunotherapy appears to correlate with administration of an optimal maintenance dose in the range of 5 to 20 μg of major allergen for inhalant allergens,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: In choosing the components for a clinically relevant allergen immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor allergens, paying special attention to potential allergens in the patient's own environment. **D**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Therefore immunotherapy merits consideration in patients with these disorders as a possible treatment option. **A**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: The potential for benefit in symptoms related to oral allergy syndrome with inhalant immunotherapy directed at the cross-reacting pollens has been observed in some studies but not in others. For this reason, more investigation is required to substantiate that a benefit in oral allergy symptoms will occur with allergen immunotherapy. **C**

Measures of efficacy. Summary Statement 12: Clinical parameters, such as symptoms and medication use, might be useful measures of the efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is not recommended. **A**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: An assessment of the patient's current health status should be made before administration of the allergy immunotherapy injection to determine whether there were any recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. **C**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: Allergen immunotherapy should be administered in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured. **C**

Patient selection

Clinical indications. Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly considered if the patient has had a systemic reaction to a Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or both and if the patient has demonstrable evidence of specific IgE antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: Skin testing has been the primary diagnostic tool in clinical studies of allergen immunotherapy. Therefore in most patients, skin testing should be used to determine whether the patient has specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, and Hymenoptera hypersensitivity. Therefore immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. Many botanically related pollens contain allergens that are cross-reactive. When pollens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily might suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent pollens might be necessary. **B**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions. It is the responsibility of each supplier or manufacturer to ship extracts under validated conditions that are shown not to adversely affect the product's potency or safety. **C**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergen immunotherapy extract expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of factors separately and collectively, including (1) storage temperature, (2) presence of stabilizers and bactericidal agents, (3) concentration, (4) presence of proteolytic enzymes, and (5) volume of the storage vial. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual allergen immunotherapy extract should be prepared from a manufacturer's extract or extracts in accordance to the patient's clinical history and allergy test results and might be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. The maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions and might not always reach the initially calculated projected effective dose. This reinforces that allergy immunotherapy must be individualized. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: Administration of an incorrect injection is a potential risk of allergen immunotherapy. An incorrect injection is an injection given to the wrong patient or a correct patient receiving an injection of an incorrect dose.

A customized individual maintenance concentrate of the allergen immunotherapy extract and serial dilutions, whether a single extract or a mixture of extracts, prepared and labeled with the patient's name and birth date might reduce the risk of incorrect (ie, wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: At present, there are no specific tests or clinical markers that will distinguish between patients who will relapse and those who will remain in long-term clinical remission after discontinuing effective inhalant allergen immunotherapy, and the duration of treatment should be determined by the physician and patient after considering the benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: Although there are no specific tests to distinguish which patients will relapse after discontinuing VIT, there are clinical features that are associated with a higher chance of relapse, notably a history of very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: The patient's response to immunotherapy should be evaluated on a regular basis. A decision about continuation of effective immunotherapy should generally be made after the initial period of up to 5 years of treatment. **D**

Summary Statement 55d: The severity of disease, benefits sustained from treatment, and convenience of treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any individual patient. **D**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: Patients at high risk of systemic reactions, where possible, should receive immunotherapy in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: In rare and exceptional cases, when allergen immunotherapy cannot be administered in a medical facility and withholding this therapy would result in a serious detriment to the patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient basis. If this approach is used, informed consent should be obtained from the patient, and the person administering the injection to the patient must be educated about how to administer immunotherapy and recognize and treat anaphylaxis. **D**

Summary Statement 63: If a patient receiving immunotherapy transfers from one physician to another, a decision must be made by the physician to whom the patient has transferred as to whether to continue immunotherapy. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program from one physician to another. In addition, a record of previous response to and compliance with this program should be communicated to the patient's new physician. **D**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in release of mediators, such as histamine, from basophils and mast cells, a phenomenon most relevant to the immediate phase of allergic reactions. Suppression of late-phase inflammatory responses in the skin and respiratory tract generally also occur with allergen immunotherapy.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] VIT resulted in a change in IgG specificity to the major bee venom allergen, phospholipase A_2, to a specificity similar to that seen in healthy nonallergic individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas serum immunoreactive specific IgG levels are not predictive, it is possible that functional assays of IgG, such as detection of IgG-associated serum inhibitory activity for IgE-facilitated allergen presentation, basophil histamine release, or both, might be more closely associated with the clinical response to immunotherapy, although this remains to be tested in larger clinical trials.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Allergen extracts are commercially available for most of the commonly recognized allergens. Allergen extract potency variability and product composition inconsistency has several potential consequences. Diagnostic allergy skin testing and allergen immunotherapy efficacy and safety are dependent on the quality of the allergen extracts. When possible, standardized extracts should be used to prepare allergen immunotherapy treatment sets.[2,18,54-56] The advantage of standardized extracts is that

the biologic activity is more consistent, and therefore the risk of an adverse reaction caused by extract potency variability should be diminished.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, short ragweed, Bermuda grass, Kentucky bluegrass, perennial rye grass, orchard grass, timothy grass, meadow fescue, red top, sweet vernal grass, and Hymenoptera venoms (yellow jacket, honeybee, wasp, yellow hornet, and white-faced hornet). However, most allergen extracts are not yet standardized. Allergen standardization comprises 2 components: (1) selection of a reference extract and (2) selection of an assay or procedure to compare the manufactured extract with the reference extract. Allergen standardization in the United States is based on assessment of the potency of allergen extracts by using quantitative skin tests and reported as BAU values. The quantitative test method is called the intradermal dilution for 50 mL sum of erythema ($ID_{50}EAL$) system for determining BAU values.[57] The $ID_{50}EAL$ method entails preparing a series of 3-fold dilutions of a candidate reference extract and injecting 0.05 mL intradermally to 15 to 20 ''highly sensitive'' allergic subjects. The dilution that results in an erythema with the sum of the longest diameter and midpoint (orthogonal) diameter equaling 50 mm is considered the end point (D_{50}). The mean D_{50} is calculated, and the potency of the extract is assigned.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g of dry allergen (eg, ragweed) was added to 100 ml of a buffer for extraction. Nonstandardized extracts can also be labeled in PNU, where 1 PNU equals 0.01 g of protein nitrogen. Neither method confers any direct or comparative information about an extract's biologic potency. Nonstandardized extracts can have a wide range of potencies. Extracts with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: In choosing the components for a clinically relevant allergen immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor allergens, paying special attention to potential allergens in the patient's own environment. **D**

Because North America is botanically and ecologically diverse, it is not possible to devise a common list of appropriate allergen extracts for each practice location. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

The clinical relevance of an aeroallergen depends on certain key properties: (1) its intrinsic allergenicity, (2) its aerodynamic properties, (3) whether it is produced in large enough quantities to be sampled, (4) whether it is sufficiently buoyant to be carried long distances, and (5) whether the plant releasing the pollen is widely and abundantly prevalent in the region. The primary allergens used for immunotherapy are derived from plant (grasses, trees, and weeds), arthropod (house dust mites), fungus, animal (cat, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Cumulative data, both *in vitro* and *in vivo*, concerning cross-reactivity offer a practical advantage in the selection of several categories of pollen allergens for immunotherapy. However, because cross-reactivity is variable for many grass and weed pollens, their intrinsic allergenicity, prevalence, and aerobiologic characteristics within a specific region should be considered. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. Because many temperate pasture grasses (subfamily Pooideae; eg, fescue, rye, timothy, blue, and orchard), which are widely distributed throughout the United States, share major allergens,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

and Bahia has become an important allergenic grass in the lower southern states. Because it is uncertain whether palms, sedges, and cattails have the ability to trigger allergy symptoms, immunotherapy with these allergens is generally not recommended.

Although cross-reactivity among tree pollens is not as pronounced as that among grass or ragweed pollens, it does occur. Pollen from members of the cypress family (Cupressaceous; eg, juniper, cedar, and cypress) strongly cross-react.[79-82] Therefore pollen from one member of this family should be adequate for skin testing and immunotherapy. The closely related birch family (Betulaceae; eg, birch, alder, hazel, hornbeam, and hop hornbeam) and oak (Fagaceae; eg, beech, oak, and chestnut) have strong cross-allergenicity.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

Ash and European olive trees are strongly cross-reactive; the extract that is the most prevalent in the region and best correlates with symptoms could be used.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *Acer*, box elders appear different and should be considered separately. Oaks and elms (eg, Chinese, Siberian, some American) are prevalent in eastern and central states but have a more limited distribution west of the continental divide. The distribution of other trees is variable enough to require botanical observation in a given locale.

There is strong cross-reactivity between major allergens of common ragweed species (eg, short, giant, false, and western). However, southern and slender ragweed do not cross-react as well,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

Weeds other than ragweed, such as marsh elders, sages, and mugwort, have an abundant distribution, predominantly in the western states. These weeds and sages (*Artemisia* species) must be treated separately from the ragweeds. Sages are strongly cross-reactive, and a single member can provide adequate coverage of the group.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] Skin testing suggests strong cross-reactivity across Chenopod and Amaranth family boundaries. The Amaranth family also seems to have strong cross-reactivity by means of RAST inhibition and immunodiffusion.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. Among other subfamily Chenopod members, Russian thistle appears to have the most cross-allergenicity.

The most prevalent house dust mites, *D pteronyssinus* and *D farinae*, are ubiquitous except in arid or semiarid climates and regions of higher altitudes. *D pteronyssinus* and *D farinae* are members of the same family and genus. They have allergens with extensive cross-reacting epitopes, as well as unique allergenic epitopes. Generally,

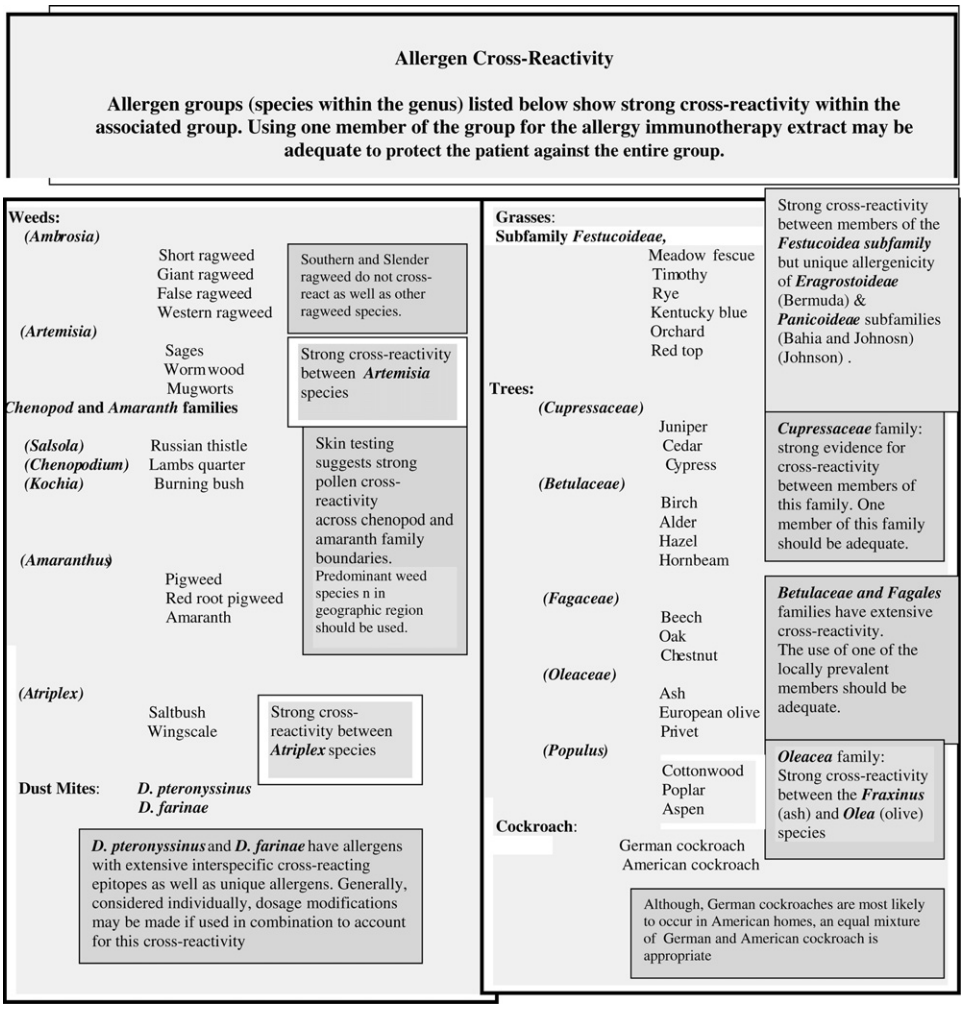


FIG 2. Patterns of allergen cross-reactivity.

D pteronyssinus and *D farinae* are considered individually. Establishing the practical importance of various allergenic fungi involves many of the same problems encountered in treating pollen allergy. In general, the genera of deuteromycetes occur in all but the coldest regions. For clinical purposes, molds often are characterized as outdoor (eg, *Alternaria*, *Cladosporium*, and *Drechslera [Helminthosporium]* species) or indoor (eg, *Aspergillus* and *Penicillium*).

Immunotherapy with standardized extracts of cat hair (Fel d 1 only) or pelt (Fel d 1 plus cat albumin) is available for cat allergy. Although German cockroaches are most likely to occur in American homes, an extract representing an equal mixture of German and American cockroaches might be appropriate for immunotherapy.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Therefore immunotherapy merits consideration in patients with these disorders as a possible treatment option. **A**

Many double-blind, placebo-controlled, randomized clinical trials demonstrate a beneficial effect of immunotherapy under a variety of conditions.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] A variety of different types of extracts have been evaluated in these clinical trials, including aqueous and modified extracts. Outcome measures used to measure the efficacy of immunotherapy include symptom and medication scores, organ challenge, and immunologic changes in cell markers and cytokine profiles. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. Although many studies demonstrate the efficacy of immunotherapy, some do not. A review of the studies that do not demonstrate efficacy failed to identify a systematic deficiency.[110] Instead, this review notes that many studies evaluating immunotherapy are only marginally powered to show efficacy, making it likely that some would fail to demonstrate efficacy by chance alone, even when it is present (a type II error). Meta-analyses of the efficacy of immunotherapy both for rhinitis[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: The potential for benefit in symptoms related to oral allergy syndrome with inhalant immunotherapy directed at the cross-reacting pollens has been observed in some studies but not in others. For this reason, more investigation is required to substantiate that a benefit in oral allergy symptoms will occur with allergen immunotherapy. **C**

The use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

In the subcutaneous peanut immunotherapy study there was increased tolerance to oral peanut challenge in all of the treated patients, but there were repeated systemic reactions in most patients, even during maintenance injections, and the authors concluded a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] One randomized, double-blind study of adults with atopic dermatitis demonstrated a dose-response effect of dust mite immunotherapy on atopic dermatitis severity, as measured by using the SCORAD score ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting pollens, has been observed in some studies but not in others. One controlled prospective study demonstrated the potential to decrease oral allergy syndrome symptoms with subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy demonstrated no significant effect on the severity of apple allergy symptoms with either method compared with the placebo group, despite a significant effect on seasonal hay fever symptoms, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: Clinical parameters, such as symptoms and medication use, might be useful measures of the efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is not recommended. **A**

Whether immunotherapy is effective can be determined by measuring objective and subjective parameters. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* IgE antibody testing of patients during immunotherapy is not recommended because it has not been demonstrated that skin test reactivity (to a single dilution) or specific IgE antibody levels correlate closely with a patient's clinical response. For that reason, most allergists rely on subjective assessments, such as a patient's report that he or she is feeling better during a season previously causing symptoms. Although subjective assessments are the most common means by which physicians judge the result of immunotherapy, they are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. Both studies found no statistical difference between the dose-adjustment and no-dose-adjustment protocols in terms of immunotherapy-induced systemic reactions. Both authors concluded that local reactions were poor predictors for subsequent systemic reactions, and dose reductions for most local reactions are unnecessary.

However, a retrospective review of a large, multicenter, allergy practice group's database comparing the frequency of large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of pollen season (46% of respondents) and immunotherapy dosing errors (25% of respondents) were cited as the 2 most important contributing factors in the NFRs. The most severe NFR was respiratory failure (10% of NFRs). One patient with an NFR was receiving a β-blocker, and none were taking concomitant angiotensin-converting enzyme inhibitors. Ninety-three percent of the NFRs occurred in clinics staffed by allergists, and none occurred in medically unsupervised settings.

In a retrospective analysis of the incidence and characteristics of nonfatal systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, there were 115 systemic reactions (5.2% of patients and 0.06% of injections) in the first 10 years and 26 systemic reactions (1.08% of patients and 0.01% of injections) in the second 10 years.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] All systemic reactions were mild to moderate and responded well to treatment.

Five patients experienced more than 3 systemic reactions (total of 36 reactions), and the authors noted that 40% of the systemic reactions (21 reactions) would have been avoided if patients experiencing the third systemic reaction had been withdrawn.

In the previously mentioned AAAAI physician members' survey of fatal reactions and NFRs, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] The estimated fatality rate was 1 per 2.5 million injections, (average of 3.4 deaths per year), which is similar to 2 previous surveys of AAAAI physician members.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: An assessment of the patient's current health status should be made before administration of the allergy immunotherapy injection to determine whether there were any recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

The most severe NFR, respiratory failure, occurred exclusively in asthmatic patients, and 4 (57%) of 7 asthmatic patients had a baseline FEV_1 of less than 70% of predicted value.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] Ten fatalities occurred during seasonal exacerbation of the patient's disease, 4 in patients who had been symptomatic at the time of the injection, 2 of whom had been receiving β-adrenergic blockers. Of the 24 fatalities associated with immunotherapy, 4 had experienced previous reactions, 11 manifested a high degree of sensitivity, and 4 had been injected with newly prepared extracts. In a prospective study of 125 asthmatic patients with mite allergy that used a 3-day rush immunotherapy protocol, FEV_1 was identified as a predictor for systemic reactions, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing an asthma reaction during rush immunotherapy, whereas only 12.6% of patients with an FEV_1 of greater than 80% of predicted value had asthmatic reactions ($P < .0001$).[191] The authors noted that if the patients with an FEV_1 of less than 80% of predicted value had been excluded from the study, the systemic reaction rate would have been 19.7% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving during periods of exacerbation of symptoms, other risk factors for immunotherapy that have been identified include the presence of a high degree of hypersensitivity, use of β-blockers, injections from new vials, and dosing errors.[17] With the exception of dosing errors and high degree of hypersensitivity, these risk factors can be minimized by performing a preinjection health screen before the administration of the allergy immunotherapy injection. This preinjection evaluation might include a health inquiry administered verbally or as a written questionnaire directed to determine whether there were any recent health changes that might require modifying or withholding that patient's immunotherapy treatment. The preinjection health inquiry might include questions regarding the presence of asthma or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

A patient's asthma must be stable before the allergen immunotherapy injection is administered, and patients with significant systemic illness generally should not receive an allergy immunotherapy injection.

Timing of anaphylactic reactions to immunotherapy injections

Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI fatal reaction and NFR surveys previously discussed, 10 (77%) patients with fatal reactions and 65 (96%) patients with NFRs, for whom information on the timing of the onset of symptoms was available, had symptoms within 30 minutes of the injection.[184,188] The onset of symptoms before the fatal immunotherapy reaction was greater than 30 minutes in 3 patients. In 1 patient the reaction began within 35 minutes after the injection, but treatment was not administered until 45 minutes after the injection. A second late reaction occurred after the patient had left the clinic early, and it was estimated that treatment was initiated at least 50 minutes after the injection. A third late reaction occurred in the office of a primary care physician and began 30 to 40

minutes after the injection, but treatment was initiated 20 minutes after the onset of symptoms. The timing of the reaction was unknown in 4 of the fatal reactions.

In an earlier AAAAI survey, 17 fatalities associated with allergen immunotherapy were reported for the years 1985-1989.[190] Onset of anaphylaxis occurred within 20 minutes in 11 patients, within 20 to 30 minutes in 1 patient, and after more than 30 minutes in 1 patient. Four patients did not wait after the injection, and the onset of their systemic reaction symptoms is not known.

In a prospective study a total of 20,588 extract injections were administered to 628 patients, resulting in 52 systemic reactions in 42 patients, with 38% of the systemic reactions occurring from 30 minutes to 6 hours after the allergy vaccine administration.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

Most of the extract manufacturers' package inserts recommend a wait period of either 20 to 30 minutes or 30 minutes after administration of the immunotherapy injection. The European Academy of Allergy and Clinical Immunology's recommended observation period after an allergen immunotherapy injection is 30 minutes.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given. The risks and benefits of continuing allergen immunotherapy in patients who have had a severe systemic reaction should be carefully considered.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- Adjust the immunotherapy dose or injection frequency if symptoms of anaphylaxis occur and immunotherapy is continued.
- Use appropriately diluted initial allergen immunotherapy extract in patients who appear to have increased sensitivity on the basis of history or tests for specific IgE antibodies.
- Instruct patients to wait in the physician's office/medical facility for 30 minutes after an immunotherapy injection. Patients at greater risk of reaction from allergen immunotherapy (eg, patients with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- Ensure procedures to avoid clerical or nursing errors (eg, careful checking of patient identification).
- Recognize that dosage adjustments downward are usually necessary with a newly prepared allergen immunotherapy extract or a patient who has had a significant interruption in the immunotherapy schedule.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. **C**

Alternatives to allergen immunotherapy should be considered in patients with any medical condition that reduces the patient's ability to survive a systemic allergic reaction. Examples include patients with markedly compromised lung function (either chronic or acute), poorly controlled asthma, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. Under some circumstances, immunotherapy might be indicated for high-risk patients, such as those with Hymenoptera venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: Allergen immunotherapy should be administered in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured. **C**

The major risk of allergen immunotherapy is anaphylaxis, which in extremely rare cases can be fatal, despite optimal management. Therefore allergen immunotherapy should be administered in a setting where anaphylaxis will be promptly recognized and treated by a physician or other health care professional appropriately trained in emergency treatment.

The health care professional who administers immunotherapy injections should be able to recognize and treat the early symptoms and signs of anaphylaxis and administer emergency treatment, if necessary. Epinephrine is the first-line treatment for anaphylaxis. Health care professionals should know the potential pharmacologic benefits, risks, and routes of administration of epinephrine, as well as the potential reasons for lack of response.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. Appropriate personnel, equipment, and medications should be immediately available to treat anaphylaxis, should it occur. Suggested actions to reduce the risk of anaphylaxis and recommended equipment and medications to treat anaphylaxis are listed in Tables V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

Indications for allergen immunotherapy in patients with reactions to Hymenoptera stings:
- patients with a history of a systemic reaction to a Hymenoptera sting (especially if such a reaction is associated with respiratory symptoms, cardiovascular symptoms, or both) and demonstrable evidence of clinically relevant specific IgE antibodies;
- patients older than 16 years with a history of a systemic reaction limited to the skin and demonstrable evidence of clinically relevant specific IgE antibodies (patients <16 years of age who present with a history of only cutaneous symptoms to Hymenoptera stings usually do not require immunotherapy);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

Allergen immunotherapy is an effective form of treatment for many allergic patients, provided they have undergone an appropriate allergy evaluation. The expected response to allergen immunotherapy is antigen specific and depends on proper identification and selection of component allergens on the basis of the patient's history, exposure, and diagnostic test results.

Aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis, rhinoconjunctivitis, and/or asthma after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. The effect of the patient's symptoms on quality of life and responsiveness to other forms of therapy, such as allergen avoidance or medication, should also be considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Patients with severe or uncontrolled asthma might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly considered if the patient has had a systemic reaction to a Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or both and if the patient has demonstrable evidence of specific IgE antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] Adults and children with a history of systemic reactions to the imported fire ant (*Solenopsis* species) who have positive skin test results or venom-specific IgE antibodies should be treated with allergen immunotherapy. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how to inject it.

Venom skin test results are positive in more than 65% of patients with a history of a systemic reaction to a Hymenoptera sting compared with 15% of the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific IgE tests, or both be repeated 3 to 6 months later. Approximately 5% to 10% of patients with negative venom skin test results with a history of a systemic reaction have a positive venom-specific IgE test result.[224] There are no published results of the effectiveness of allergen immunotherapy in patients with negative skin test results and positive venom-specific IgE test results who have experienced systemic reactions resulting from a Hymenoptera sting. There are data to indicate that these patients might have another episode of anaphylaxis if they are re-stung. The chance of another systemic reaction to a sting is relatively small (5% to 10%) in adults with negative venom skin test results with a history of systemic reactions compared with the risk associated with positive venom skin test results (25% to 70%).[225] However, even though the risk is small, the reaction can be severe, and VIT is recommended for patients with negative venom skin test results and positive venom-specific IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very few anecdotal reports of patients with negative venom skin test results and negative venom-specific IgE test results being successfully treated with VIT if the selected venom is based on the results of a sting challenge. Generally, there are not sufficient data on the efficacy of immunotherapy in these patients to form conclusive recommendations.

The AAAAI Insect Committee's modified working guidelines state that a negative venom skin test result or *in vitro* assay result is not a guarantee of safety, and patients with suspected higher risk should be counseled about avoidance strategies, use of epinephrine injectors, and the emergency and follow-up care of the acute allergic reaction.[226] The AAAAI Insect Committee also acknowledged that the management of patients with a positive history and negative venom skin test results requires clinical judgment and ongoing research.

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Patients who are mentally or physically unable to communicate clearly with the physician and patients who have a history of noncompliance might be poor candidates for immunotherapy. If a patient cannot communicate clearly with the physician, it will be difficult for the patient to report signs and symptoms, especially early symptoms, suggestive of systemic reactions.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), animal dander, dust mite, and cockroach, is required in the selection of the components for a clinically relevant allergen immunotherapy extract. Although the relationship between day-to-day outdoor pollen and fungi exposure and the development of clinical symptoms is not always clear, symptoms that occur during periods of increased exposure to allergens, in association with positive skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. As is the case in interpreting positive immediate hypersensitivity skin test results, there must be a clinical correlation with the demonstration of *in vitro* allergen-specific IgE levels and clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* testing, as is being done by both commercial laboratories and some physician's offices. This is promoting the remote practice of allergy, which is not recommended.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The inclusion of all allergens to which IgE antibodies are present, without establishing the possible clinical relevance of these allergens, might dilute the content of other allergens in the allergen immunotherapy extract and can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. A patient's lifestyle can produce exposure to a wide variety of aeroallergens from different regions, necessitating inclusion in the extract of multiple allergens from different geographic areas. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes of asthmatic children. In the National Cooperative Inner-City Asthma Study, 33% of the homes had detectable rat allergen (Rat n 1), and a correlation between rat allergen sensitization with increased asthma morbidity in inner-city children was found.[231] Fur-bearing pets and the soles of shoes are also conduits by which molds and other ''outdoor'' allergens can enter the home.

Several commercial immunoassays to measure the presence of indoor allergens (eg, dust mite, cat, cockroach, and dog) in settled house dust samples are available and might provide useful estimates of indoor allergen exposure. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: Skin testing has been the primary diagnostic tool in clinical studies of allergen immunotherapy. Therefore in most patients, skin testing should be used to determine whether the patient has specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

The use of standardized allergens has greatly increased the consistency of skin test results for these antigens. Controlled studies in which the clinical history has correlated with the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] Skin testing can also provide the physician with useful information about the appropriate starting dose of selected allergens. On rare occasions, systemic reactions can occur from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of these reasons, skin testing is preferable as a method for selection of allergens for inclusion in immunotherapy and determining the starting dose for an immunotherapy program. Among the skin testing techniques available, a properly applied percutaneous (prick/puncture) test consistently produces reproducible results. Generally, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. In the case of Hymenoptera venom, immunotherapy can be started even without a live sting challenge in patients with negative skin test results and positive *in vitro* test results. However, there are no published results of the effectiveness of Hymenoptera VIT in patients with negative skin test results and positive *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, and

Hymenoptera hypersensitivity. Therefore immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens, as supported by the presence of specific IgE antibodies. **A**

Pollen. Pollen extracts have been shown to be safe and effective in many controlled clinical trials.[17,104,106,107,109] It seems reasonable to extrapolate information about pollen extracts that have been studied to those that have not been subjected to rigorous investigation and to assume that the latter are also safe and effective. Less information is available with respect to mixtures of pollen extracts. However, those studies that have been conducted with mixtures have demonstrated clinical effectiveness.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] For example, there are no commercially available extracts for many fungal ascospores, even though they frequently are the dominant type of airborne bioparticulate during certain seasons. Another example is the lack of basidiospore (mushroom) extracts, especially given the evidence that such exposures can be associated with epidemics of asthma in the late fall. It is important that the practicing physician distinguish between molds that are predominantly found indoors (eg, *Penicillium* and *Aspergillus* genera) and many other molds that are found either exclusively outdoors or both indoors and outdoors and be able to assess the potential clinical effect of each.

Animal dander. Although the best treatment for animal allergy is avoidance, this is not always possible. Exposure to both dog and cat allergen has been shown to be ubiquitous and can occur even without an animal in the home, making avoidance even more difficult.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D pteronyssinus* contain 2 major allergen groups that are immunologically cross-reactive: Der p 1 and Der f 1 and Der p 2 and Der f 2. Sixty percent or more of mite-sensitive patients react to these 2 major allergen dust mite groups. Allergens from other species of mites, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need to be included when preparing an allergen immunotherapy extract based on the high degree of cross-allergenicity between the major allergens in these 2 species. Immunotherapy for dust mites is effective[144,147-149,151] and should be considered in conjunction with avoidance measures in patients who have symptoms consistent with dust mite allergy and specific IgE antibodies for dust mite allergens. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

The most common species of cockroach identified in dwellings are the German cockroach, *Blatella germanica*, and the American cockroach, *Periplaneta americana*. Allergens derived from *B germanica* include Bla g 2, Bla g 4, and Bla g 5. The major allergen of *P americana* is Per a 1. Partial cross-reactivity between cockroach allergens exists, but each regionally relevant species should be represented in the immunotherapy extract.[243] Immunotherapy with cockroach allergens is effective[154] and should be considered in conjunction with aggressive avoidance measures, particularly in patients living in the inner city who have perennial allergic symptoms and specific IgE antibodies to cockroach allergens.

Hymenoptera venom. Randomized, double-blind, placebo-controlled studies show that immunotherapy with Hymenoptera venom is effective in dramatically reducing the risk of anaphylaxis to honeybee, yellow jacket, hornet, and wasp stings.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of factors need to be considered

when combining extracts, including (1) cross-reactivity of allergens, (2) the need to include the optimal dose for each constituent, and (3) potential interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. Many botanically related pollens contain allergens that are cross-reactive. When pollens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily might suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent pollens might be necessary. **B**

Immunologic and allergenic cross-reactivity is the recognition by the patient's immune system of different extracts' constituents as the same or similar. When one allergen elicits the same immunologic responses as another cross-reacting allergen, it is not necessary or even desirable to include both in the same mixture.[71] Such a practice might result in the addition of too much of a given allergen, which could lead to an adverse reaction, as well as the unnecessary dilution of other allergens, with a resultant reduction in efficacy. A knowledge of each allergen's classification according to species and the fact that there is immunologic cross-reactivity within allergens of the same genera or subfamily allows one to select components of the allergen immunotherapy extract that are maximally effective. In general, the patterns of allergenic cross-reactivities among pollens follow their taxonomic relationships (see the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

The maintenance dose of allergen immunotherapy must be adequate.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **B**

Many allergen extracts contain mixtures of proteins and glycoproteins. Proteolytic enzymes can degrade other allergenic proteins. There have been reports of interactions between extracts when mixed together.[240,246,247] Extracts such as *Alternaria* species have been shown to reduce the IgE-binding activity of timothy grass extract when mixed together. Studies designed to investigate the effect of combining mold/fungi extracts with pollen extracts have demonstrated a significant loss of potency of grass pollen, cat, birch, white oak, box elder, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] but another study found short ragweed Amb a 1 was susceptible to proteases present in *Penicillium* and *Alternaria* species extracts at relatively low (10%) glycerin levels.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. The effect of the combination of high proteolytic-containing extracts on each other or the extent of self-degradation of allergenic proteins has not been extensively studied. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

Because such interactions between extracts have not been fully delineated, consideration should be given to keeping extracts that tend to have high proteolytic enzyme activities, such as fungi and cockroach extracts, separate from those with lesser activities, such as pollen extracts.

It is not recommended to mix venoms together (eg, wasps or honeybee with yellow jacket), even though yellow jacket and hornet venom are available premixed as a mixed-vespid extract.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly inappropriate for allergenic products. For example, substitution with differing lots, manufacturers, or dose formulations might be routine for conventional drugs and medications but could lead to fatal anaphylactic reactions with allergenic products. Prepared allergenic products usually have expiration dates of 3 to 12 months from the date of preparation but should not extend beyond the shortest expiration date of the individual components. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP Allergen Immunotherapy Extract Preparation Guidelines

1. **Qualifications of extract preparation personnel**:
   - Compounding personnel must pass a written test on aseptic technique and extract preparation.
   - Compounding personnel must be trained in preparation of allergenic products.
   - Compounding personnel must annually pass a media-fill test, as described below.*
   - Compounding personnel who fail written or media-fill tests would be reinstructed and re-evaluated.
   - Compounding personnel must be able to demonstrate understanding of antiseptic hand cleaning and disinfection of mixing surfaces.
   - Compounding personnel must be able to correctly identify, measure, and mix ingredients.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if phenol concentration is less than 0.25%, the extract must have a glycerin concentration of at least 20%.
4. **Dilutions prepared in accordance with manufacturer's instructions**: Allergen extracts must be diluted in accordance with the antigen manufacturer's instructions.
5. **Potency**: The manufacturer's expiration dates must be followed. Beyond-use dates for allergy extract dilutions should be based on the best available clinical data.
6. **Mixing of extracts with high and low proteolytic enzymes—cross-reactivity of antigens**: Separation of aqueous extracts with high proteolytic enzyme activities from other extracts is recommended.
7. **Storage**: Extracts should be stored at 4°C to reduce the rate of potency loss or according to the manufacturer's directions. Extracts beyond the expiration date of the manufacturer are to be discarded. Storage must be in a designated refrigerator for medications and not used for food or specimens.
8. **Subcutaneous injection**: Allergen extracts can only be administered intradermally or through subcutaneous injection unless the FDA-approved package insert or accepted standards of clinical practice permit another route of administration.
9. **Aseptic technique**: Preparation of allergy immunotherapy shall follow aseptic manipulations defined as follows:
   - The physician must designate a specific site, such as a countertop, in an area of the practice facility where personnel traffic is restricted and activities that might contribute to microbial contamination (eg, eating, food preparation, and placement of used diagnostic devices and materials and soiled linens) are prohibited.
   - The extract preparation area must be sanitized with 70% isopropanol that does not contain added ingredients, such as dyes and glycerin.
   - Extract preparation personnel must thoroughly wash hands to wrists with detergent or soap and potable water. Substitution of hand washing by treatment with sanitizing agents containing alcohol and/or 70% isopropanol is acceptable.
   - Necks of ampules to be opened and stoppers of vials to be needle punctured must be sanitized with isopropanol.
   - Direct contact contamination of sterile needles, syringes, and other drug-administration devices and sites on containers of manufactured sterile drug products from which drugs are administered must be avoided. Sources of direct contact contamination include, but are not limited to, touch by personnel and nonsterile objects, human secretions, blood, and exposure to other nonsterile materials.
   - After mixing is complete, visual inspection is to be performed for the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and beyond-use date of the vial.
11. **Mixing log**: A mixing log is to be kept with information on the patient's name, extract used for mixing, mixing date, and expiration date and lot numbers.
12. **Policy and procedure manual**: Practices preparing allergy extracts must maintain a policy and procedure manual for the procedures to be followed in mixing, diluting, or reconstituting of sterile products and for the training of personnel in the standards described above.

*__Example of a media-fill test procedure__: This or an equivalent test is performed at least annually by each person authorized to compound allergen immunotherapy extracts under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of allergen immunotherapy extracts. Once begun, this test is completed without interruption.
A double-concentrated media, such as from Valiteq (http://www.valiteq.com), is transferred in ten 0.5-mL increments with a sterile syringe to a sterile 10-mL vial. Five milliliters of sterile water (preservative free) is added. This is the concentrate. The vial is incubated within a range of 20°C to 35°C for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions. It is the responsibility of each supplier or manufacturer to ship extracts under validated conditions that are shown not to adversely affect the product's potency or safety. **C**

Because the efficacy and safety of immunotherapy depend on the use of allergen immunotherapy extracts with reasonably predictable biologic activity, it is important that they be stored under conditions that preserve such activity. The potency of allergen immunotherapy extracts is affected by a number of factors, including the passage of time, temperature, concentration, number of allergens in a vial, volume of the storage vial, and presence of stabilizers and preservatives. Allergen immunotherapy extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. The results of these studies are on file under each manufacturer's product licenses. Each study is specific to each manufacturer because the packaging (eg, use of insulation) varies from company to company. It is the responsibility of each supplier or manufacturer to ship allergen extracts under validated conditions that have been shown not to adversely affect the product's potency or safety.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of factors separately and collectively, including (1) storage temperature, (2) presence of stabilizers and bactericidal agents, (3) concentration, (4) presence of proteolytic enzymes, and (5) volume of the storage vial. **D**

The potency of concentrated allergen immunotherapy extracts (1:1 vol/vol up to 1:10 vol/vol) when kept at 4°C is relatively constant and allows the allergen immunotherapy extract to be used until the expiration date that is present on the label. Less concentrated allergen immunotherapy extracts are more sensitive to the effects of temperature and might not maintain their potency until the listed expiration date.[249,250]

The mixing of other allergens might decrease the loss of potency with time because the additional allergens might prevent adherence of proteins to the vial's glass wall. Thus highly concentrated extracts are more stable than diluted ones. Extracts are prepared as aqueous, glycerinated, freeze-dried, and alum formulations. Aqueous and glycerin diluents are compatible for mixing standardized with nonstandardized products. Lyophilization is used to maintain the strength of the dry powder, but once the allergen immunotherapy extract is reconstituted, stabilizing agents, such as human serum albumin (0.03%) or 50% glycerin, are needed to maintain potency.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] Human serum albumin might also prevent the loss of potency within storage vials by preventing absorption of allergen on the inner surface of the glass vial. Glycerin is also a preservative. At a concentration of 50%, glycerin appears to prevent loss of allergenic potency,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. The extract manufacturers' package insert advises care when administering a volume greater than 0.2 mL of an extract in 50% glycerin because of the potential discomfort and pain it might cause. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI Immunotherapy and Allergy Diagnostic committee designed to study the stability of a mixture of standardized extracts in 4 conditions of storage (with and without intermittent room temperature exposure and diluted in normal saline or human serum albumin) found that short ragweed at 1:10 vol/vol dilution, as measured by means of radial immunodiffusion, was stable in all conditions of storage over 12 months. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using an mAb for Der p 1, Der f 1, and Fel d 1.

The expiration date of any dilution should not exceed the expiration date of the earliest expiring constituent that is added to the mixture.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual allergen immunotherapy extract should be prepared from a manufacturer's extract or extracts in accordance to the patient's clinical history and allergy test results and can be based on single or multiple allergens. **D**

An allergen extract is a solution of elutable materials derived from allergen source materials, such as pollens or molds. They consist of complex mixtures of proteins and glycoproteins to which antibodies can bind. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

Extracts obtained from extract manufacturing companies should be called the manufacturer's extract. Vials of manufacturer's extract contain individual or limited

mixtures of allergens that can be used alone as a concentrated dose of single allergen or combined with other concentrated allergens to prepare an individual patient's customized allergen mixture. This is designated as the patient's maintenance concentrate.

Nonstandardized manufacturer's extracts usually are available at concentrations of between 1:10 and 1:50 wt/vol or 20,000 and 100,000 PNU. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 30,000 AU for dust mite; and 100,000 AU or 1:10 and 1:20 wt/vol for short ragweed, with the Amb a 1 concentration listed in FDA units on the label of the wt/vol extracts (Table IX). The main factor that limits how concentrated an allergen immunotherapy extract can be is the tendency of highly concentrated antigen solutions to develop precipitates. This is an unpredictable and poorly understood phenomenon. Although there is no evidence that such precipitates adversely affect the extract, the FDA does not permit a manufacturer to ship an extract that has a precipitate.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. The maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions and might not always reach the initially calculated projected effective dose. This reinforces that allergy immunotherapy must be individualized. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. The maintenance concentrate (if a mixture of extracts) should either be obtained from the manufacturer as a customized mixture or should be prepared by the physician under sterile conditions by adding an appropriate volume of individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, the original projected maintenance concentration of the allergen immunotherapy extract is still referred to as the maintenance concentrate, and the specific patient's therapeutic dose is referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens that have not been standardized, the effective dose must be estimated and individualized. It is important to keep a separate record of the contents of each extract, including final dilutions of each of the constituents. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. Although early improvement in symptoms has been documented with these doses, long-term benefit appears to be related not only to the individual maintenance dose but also the duration of time that it is administered.[14]

Because a full dose-response curve has not been determined for most allergens, it is possible (and supported by expert opinion) that therapeutic response can occur with doses lower than those that have been shown to be effective in controlled studies. In general, however, low doses are less likely to be effective, and very low doses usually are ineffective.[27] Although administration of a higher maintenance dose of immunotherapy increases the likelihood of clinical effectiveness, it also increases the risk of systemic reactions. In particular, highly sensitive patients might be at risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals who have systemic reactions with doses that are less than the projected effective dose should be maintained on the highest tolerated dose, providing this dose is effective. The highest tolerated effective therapeutic dose is referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 extracts licensed in the United States are standardized based on major allergen content (measured by means of radial immunodiffusion): short ragweed (Amb a 1) and cat (Fel d 1).

[b]The labeled concentrations for the nonstandardized extracts have no established standards for biologic potency. Nonstandardized extracts are labeled on the basis of PNU values or the weight of the source material extracted with a given volume of extracting fluid (wt/vol).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. One study designed to investigate the effect of 3 doses of an alum-precipitated *D pteronyssinus* extract (0.7, 7, and 21 μg of Der p 1) found a dose-response effect on efficacy and side effects.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. Appropriate dose reductions would need to be made when combining antigens that have a strong degree of cross-reactivity, such as *D pteronyssinus* and *D farinae*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–licensed grass pollen extracts contain a table to convert the nonstandardized units (wt/vol and PNU), for which there have been studies that have demonstrated efficacy, into BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. Appropriate dose reductions would need to be made when combining antigens that have a strong degree of cross-reactivity, such as the northern pasture grasses (subfamily Pooideae; eg, perennial rye, meadow fescue, or timothy).

[f]Ragweed is reported in FDA units, with 1 U of Amb a 1 equaling 1 μg of Amb a 1. The potency units for short ragweed extracts were originally assigned based on their Amb a 1 content. Subsequent data suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated a significant improvement in ragweed nasal challenge in patients treated with a mean dose of 6 μg of Amb a 1 for 3 to 5 years compared with an untreated matched control group.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] The 3-μg dose also demonstrated significant efficacy, although not as great as the 15-μg dose. The extract used in the dosing study was assayed at 160 μg/mL. Subsequent lots have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

The more antigens that are added to the maintenance concentrate, the more there is the potential to dilute other antigens in the vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

TABLE XI. Procedure for dilutions from the maintenance concentrate (which is termed 1:1 vol/vol)

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
1:1 (vol/vol)	1.0	0.0	1.0	1:1 (vol/vol)
1:1 (vol/vol)	2.0	8.0	10.0	1:5 (vol/vol)
1:1 (vol/vol)	1.0	9.0	10.0	1:10 (vol/vol)
1:10 (vol/vol)	1.0	9.0	10.0	1:100 (vol/vol)
1:100 (vol/vol)	1.0	9.0	10.0	1:1000 (vol/vol)

All dilutions are expressed as vol/vol from the maintenance concentrate.

If the appropriate concentration of each allergen extract is added, then adding additional allergens to the maintenance concentration will have no effect on the concentration of the other allergens, as long as the additional allergens are replacing diluent. For example, if the desired maintenance concentration for cat is 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 BAU/mL in both mixtures. Once the diluent is all replaced, addition of further allergens will result in undesirable dilution of all allergens in the maintenance mixture.

Dilutions of the maintenance concentrate

Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

In preparation for the build-up phase of immunotherapy, serial dilutions should be produced from each maintenance concentrate. Typically, these are 10-fold dilutions, although other dilutions occasionally are used. These dilutions should be labeled in terms of vol/vol to indicate that they are dilutions derived from the maintenance concentrate. For example, serial 10-fold dilutions from the maintenance concentrate would be labeled as 1:10 (vol/vol) or 1:100 (vol/vol). Alternatively, the vial dilutions can be labeled in actual units (eg, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts dilutions are shown in Table XI. If the final volume of the diluted allergen immunotherapy extract to be produced is 10 mL, then one tenth of that final volume, or 1.0 mL, should be removed from the more concentrated allergen immunotherapy extract and added to a new bottle containing 9.0 mL of diluent.

Labeling dilutions

Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

During the build-up phase of immunotherapy, a number of dilutions of the patient's maintenance concentrate are needed. Use of one labeling system to indicate dilutions might help to avoid administration errors (Table XII). In addition to the labeled dilution from the maintenance concentrate (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels system is used, it is essential that it be used in the same way by all physicians to reduce potential administration errors by staff unfamiliar with the labeling system. If the current labeling system is different, the transition toward the uniform labeling system should be gradually phased in to reduce potential errors, and the staff involved with preparation and administration of allergen immunotherapy should be involved with the planning of this transition.

TABLE XII. Suggested nomenclature for labeling dilutions from the maintenance concentrate

Dilution from maintenance concentrate	Vol/vol label	No.	Color
Maintenance concentrate	1:1	1	Red
10-fold	1:10	2	Yellow
100-fold	1:100	3	Blue
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

If a numbering system is used, the highest concentration should be numbered 1. This is necessary to provide consistency in labeling because if larger numbers are used to indicate more concentrated extracts, the number of the maintenance concentrate would vary from patient to patient depending on the number of dilutions made. If a color-coding system is used, it should be consistent (eg, the highest concentration should be red, the next highest yellow, followed by blue, green, and silver in that order) (Figs 3 and 4).

Regardless of the labeling system used for indicating dilutions from the maintenance concentrate, the specific contents of each allergen immunotherapy extract should be listed separately. The volume and concentration of each of its constituents should be listed on the immunotherapy prescription form.

Consistency is essential as a basis for adoption of a standardized system. Some allergists/immunologists, however, have found it helpful to use letters for designating different component mixtures of extracts (eg, trees [T], grasses [G], and molds [M] [see Appendix 2]).

Individualized treatment vials

Summary Statement 41: Administration of an incorrect injection is a potential risk of allergen immunotherapy. An incorrect injection is an injection given to the wrong patient or a correct patient receiving an injection of an incorrect dose.

A customized individual maintenance concentrate of the allergen immunotherapy extract and serial dilutions, whether a single extract or a mixture of extracts, prepared and labeled with the patient's name and birth date might reduce the risk of incorrect (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Individually prepared and labeled vials are recommended because they have several potential advantages over shared vials (ie, vials of allergen extract used for multiple patients). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] The risk of errors of administration might be reduced because the individually prepared allergen immunotherapy vials labeled with the patient's name and birth date will allow the person administering the extract and the patient an opportunity to verify the name/birth date on the label before administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] The incorrect injections resulted in 1 death, 29 hospital admissions, and 59 emergency department visits. In addition to patient identifiers on vial labels, the authors cited several reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

There are 2 phases of allergen immunotherapy administration: the initial build-up phase, when the dose and concentration of allergen immunotherapy extract are slowly increased, and the maintenance phase, when the patient receives an effective therapeutic dose over a period of time. If the starting dose is too dilute, an unnecessarily large number of injections will be needed, resulting in a delay in achieving a therapeutically effective dose. On the other hand, if the starting dose is too concentrated, the patient might be at increased risk of having a systemic reaction.

When choosing the starting dose, most allergists/immunologists start at a dilution of the maintenance concentrate that is appropriate based on the sensitivity of the patient to the allergens in the extract, which in turn is based on the history and skin test reactivity.

Common starting dilutions from the maintenance concentrate are 1:10,000 (vol/vol) or 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

A number of schedules are used for the build-up phase of immunotherapy. The most commonly used schedule is for increasing doses of allergen immunotherapy extract to be administered 1 to 2 times per week. This weekly schedule is recommended in most of the allergen extract package inserts. With this schedule, a typical patient can expect to reach a maintenance dose in 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

Allergen immunotherapy extracts used during the build-up phase usually consist of three or four 10-fold dilutions of the maintenance concentrate. The volume generally is increased at a rate that depends on a number of factors, including (1) the patient's sensitivity to the

extract, (2) the history of prior reactions, and (3) the concentration being delivered (with smaller percentage increments being given at higher concentrations).

Dose adjustments for systemic reactions

Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

It is customary to either reduce the dose if a systemic reaction has occurred or consider discontinuation of immunotherapy, especially if the reaction has been severe. Although there are no evidence-based guidelines on dose adjustment after a systemic reaction, many allergists/immunologists reduce the dose to one that was previously tolerated or an even lower dose if the reaction was severe. Once the patient tolerates a reduced dose, a cautious increase in subsequent doses can be attempted. It is important for the physician who prescribed the allergen immunotherapy extract to review the course of immunotherapy to determine whether the benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction, especially if the patient is experiencing a significant exacerbation of symptoms and, in particular, asthma symptoms.[184] Therefore it is reasonable to consider not increasing or even reducing the dose of the allergen immunotherapy extract during seasons when the patient is exposed to increased levels of allergen to which they are sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

During the build-up phase, it is customary to repeat or even reduce the dose of allergen immunotherapy extract if there has been a substantial time interval between injections. This depends on (1) the concentration of allergen immunotherapy extract that is to be administered, (2) whether there is a previous history of systemic reactions, and (3) the degree of variation from the prescribed interval of time, with longer intervals since the last injection leading to greater reductions in the dose to be administered (see Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Cluster schedules are designed to accelerate the build-up phase of immunotherapy. Cluster immunotherapy usually is characterized by visits for administration of allergen immunotherapy extract 1 or 2 times per week with a schedule that contains fewer total injections than are used with conventional immunotherapy. With cluster immunotherapy, 2 or more injections are given per visit on nonconsecutive days (see Appendix 5).[22,26] The injections are typically given at 30-minute intervals, but longer intervals have also been used in some protocols. This schedule can permit a patient to reach a maintenance dose in as brief a period of time as 4 weeks. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Rush schedules are more rapid than cluster immunotherapy. An early study used a schedule that permitted patients to achieve a maintenance dose in 6 days; however, patients were required to remain in the hospital.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] The advantage of a cluster or rush schedule is that it permits patients to attain a therapeutically effective maintenance dose more rapidly than with a conventional schedule. Controlled studies have shown symptomatic improvement shortly after reaching maintenance doses by using cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

Systemic reactions with rush schedules have been reported to occur up to 2 hours after the final injection. For that reason, individuals receiving rush immunotherapy should remain under physician supervision for a longer waiting period than the usual 30 minutes recommended for conventional schedules (eg, 1.5-3 hours on the day of allergen immunotherapy extract administration).

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. However, one randomized controlled study demonstrated that premedication reduced the frequency of severe systemic reactions caused by conventional immunotherapy and increased the proportion of patients who achieved the target maintenance dose.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite premedication treatment. Because many patients might take an antihistamine as part of their overall allergy management, it is important to determine whether they have taken it on the day that they receive an allergen immunotherapy extract injection. For consistency in interpretation of reactions, it also might be desirable that they consistently either take their antihistamine or avoid it on days when they receive immunotherapy. Other attempts to reduce the occurrence of systemic reactions, such as the addition of epinephrine to the allergen immunotherapy extract or use of concomitant corticosteroids, are not justified and might delay the onset of a systemic reaction beyond the waiting time when the patient is in the physician's office, thus increasing the risk.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Premedication with a nonsedating antihistamine (loratadine) 2 hours before the first injection of each visit reduced both the number and severity of systemic reactions during cluster immunotherapy.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Once a patient who is receiving inhalant allergen immunotherapy reaches a maintenance dose, an interval of 2 to 4 weeks between injections is recommended, provided clinical improvement is maintained. Some individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. In other patients, greater efficacy, fewer reactions, or both might occur with shorter intervals between injections. Therefore the interval between allergen immunotherapy injections should be individualized to provide the greatest efficacy and safety for each patient.

Continuing care

Time course of improvement. Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. If clinical improvement is not apparent after 1 year of maintenance therapy, possible reasons for lack of efficacy should be evaluated. If none are found, discontinuation of immunotherapy should be considered, and other treatment options should be pursued.

Follow-up visits. Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

Patients should be evaluated at least every 6 to 12 months while receiving immunotherapy:

- to assess efficacy;
- to implement and reinforce its safe administration and to monitor adverse reactions;
- to assess the patient's compliance with treatment
- to determine whether immunotherapy can be discontinued; and
- to determine whether adjustments in immunotherapy dosing schedule or allergen content are necessary.

Patients might need more frequent office visits for evaluation and management of immunotherapy (eg, treatment of local reactions, systemic reactions, or both or changes in their immunotherapy vials or lots) or changes in the management of underlying allergic disease or comorbid conditions.

Duration of treatment

Summary Statement 55a: At present, there are no specific tests or clinical markers that will distinguish between patients who will relapse and those who will remain in long-term clinical remission after discontinuing effective inhalant allergen immunotherapy, and the duration of treatment should be determined by the physician and patient after considering the benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: Although there are no specific tests to distinguish which patients will relapse after discontinuing VIT, there are clinical features that are associated with a higher chance of relapse, notably a history of very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: The patient's response to immunotherapy should be evaluated on a regular basis. A decision about continuation of effective immunotherapy should generally be made after the initial period of up to 5 years of treatment. **D**

Summary Statement 55d: The severity of disease, benefits sustained from treatment, and convenience of treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any individual patient. **D**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. The severity of disease, benefits sustained from treatment, and convenience of treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any individual patient. If allergen immunotherapy is effective, treatment might be continued for longer than 3 years, depending on the patient's ongoing response to treatment. Some patients experience a prolonged remission after discontinuation, but others might relapse after discontinuation of immunotherapy. Therefore the decision to continue or stop immunotherapy must be individualized.

There have been very few studies designed specifically to look at the question of when to discontinue effective allergen immunotherapy or the duration of immunotherapy efficacy after termination of treatment. The duration of allergen immunotherapy efficacy has probably been most extensively studied in Hymenoptera hypersensitivity. Long-term follow-up studies suggest that a 5-year immunotherapy treatment course for Hymenoptera hypersensitivity might be sufficient for most allergic individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested that a 3- to 5-year treatment duration is sufficient for inhalant allergen immunotherapy, but others

have reported a significant relapse rate within 3 years of discontinuing allergen immunotherapy.

One prospective controlled study was designed to study the immunotherapy relapse rate during the 3-year period after discontinuation of immunotherapy in 40 asthmatic patients who had been treated with immunotherapy with a standardized dust mite *(D pteronyssinus)* extract for 12 to 96 months.[14] Fifty-five percent of the patients relapsed. The duration of efficacy was related to the reduction of skin test reactivity at the end of immunotherapy treatment ($P = .003$) and the duration of immunotherapy treatment. The relapse rate was 62% in the group treated for less than 35 months compared with 48% in the group treated for greater than 36 months ($P = .04$). Prolonged clinical efficacy was demonstrated in a double-blind, placebo-controlled study of patients with severe grass pollen–induced allergic rhinitis who had been treated for 3 to 4 years with immunotherapy.[13] There was a switch to placebo in half of the group (16 patients) after 3 to 4 years of immunotherapy, and efficacy parameters were monitored over the next 3 years. Seasonal symptom scores and the use of rescue medication remained low for 3 to 4 years after the discontinuation of immunotherapy, and there was no significant difference between patients who continued and those who discontinued immunotherapy. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and the duration of treatment should be determined by the physician and patient after considering the benefits and risks associated with discontinuing or continuing inhalant immunotherapy.

A form to document indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

An immunotherapy injection should not be given unless adequate documentation is available in the patient's medical record. This also means that patients who receive injections in a health care facility other than the office of the prescribing physician must have appropriate documentation. The recommended documentation for informed consent allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-inch nonremovable needle. Syringes specifically designed for immunotherapy are available from medical supply companies. Although recent Occupational Safety and Health Administration guidelines mandate the use of safety needles with allergy injections, recent publications indicate a potential increase in accidental needle sticks with the use of safety needles compared with standard syringes.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper arm at the junction of the deltoid and triceps muscles. This location tends to have a greater amount of subcutaneous tissue than adjacent areas. The skin should be wiped with an alcohol swab before giving the immunotherapy injection. This does not sterilize the area, but it does remove gross contamination from the skin surface.

Immunotherapy should be given subcutaneously. Subcutaneous injections result in formation of a reservoir of allergen immunotherapy extract that is slowly absorbed. Absorption that is too rapid, such as after an intramuscular injection, could lead to a systemic reaction. The skin should be pinched and lifted off of the muscles to avoid intramuscular or intravenous injection and to increase access to the subcutaneous tissues.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, the syringe should be removed and discarded in an appropriate container (''sharps'' box). Another dose of the allergen extract should be drawn into a new syringe and a different site chosen for the injection. In theory, removal of the syringe when blood is present reduces the likelihood of intravenous administration, which could lead to a systemic reaction. The syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

The plunger should be depressed at a rate that does not result in wheal formation or excessive pain. Mild pressure should then be applied to the injection site for about 1 minute immediately after removal of the needle. This reduces the chance of leakage of the allergen extract, which could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

The preferred location of allergen immunotherapy administration is in the office of the physician who prepared the patient's allergen immunotherapy extract. The physician's office should have the expertise, personnel, and procedures in place for the safe and effective administration of immunotherapy. However, in many cases it might be necessary to administer the allergen immunotherapy extract in another physician's office. Allergen immunotherapy should be administered with the same care wherever it is administered. A physician or qualified physician extender to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: Patients at high risk of systemic reactions, where possible, should receive immunotherapy in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Patients at high risk of systemic reactions (highly sensitive, severe symptoms, comorbid conditions, and history of recurrent systemic reactions), where possible, should receive immunotherapy in the allergist/immunologist's office.[292] The allergist/immunologist who prepared the patient's allergen immunotherapy extract and his or her support staff should have the experience and procedures in place for the administration of allergen immunotherapy to such patients.[184] The early signs of an allergic reaction are more likely to be recognized and early treatment initiated, which will decrease the possibility of a serious outcome. Modifications might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

The physician and personnel administering immunotherapy should be aware of the technical aspects of this procedure and have available appropriately trained personnel, resuscitative equipment/medicines, and storage facilities for allergen immunotherapy extract.[292] The health care professional and staff should be able to recognize early signs and symptoms of anaphylaxis and administer emergency medications as necessary.

The physician and staff should be aware of situations that might place the patient at greater risk for systemic reactions (eg, concomitant medications that can interfere with emergency treatment, such as β-blockers, acute illness, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

Any systemic reaction to allergen immunotherapy should be treated immediately, and the physician who prepared the allergen immunotherapy extract should be informed. This might require a return to the allergist/immunologist's office for treatment and re-evaluation.

Home administration. Summary Statement 62: In rare and exceptional cases, when allergen immunotherapy cannot be administered in a medical facility and withholding this therapy would result in a serious detriment to the patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient basis. If this approach is used, informed consent should be obtained from the patient, and the person administering the injection to the patient must be educated about how to administer immunotherapy and recognize and treat anaphylaxis. **D**

Allergen immunotherapy should be administered in a medical facility with trained staff and medical equipment capable of recognizing and treating anaphylaxis. Under rare circumstances, when the benefit of allergen immunotherapy clearly outweighs the risk of withholding immunotherapy (eg, patients with a history of venom anaphylaxis living in a remote region), at-home administration of allergen immunotherapy can be considered on an individual basis. In this instance there should be a discussion with the patient with very careful consideration of the potential benefits and risks involved in home administration and alternatives. Informed consent should be obtained from the patient and appropriate family members after this discussion. Under these circumstances, another adult person should be fully trained to administer the injection and to treat anaphylaxis if this should occur. It should be noted, however, that the package insert approved by the FDA that accompanies all allergen extracts, including venom, implies that allergy injections should be administered in a clinical setting under the supervision of a physician. Intuitively, the risk from administering allergenic extracts outside a clinical setting would appear to be greater. Recognition and treatment of anaphylaxis might be delayed or less effective than in a clinical setting in which supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). Home administration should only be considered in the rare circumstance when the benefit of immunotherapy clearly outweighs the risks. Frequent or routine prescription of home immunotherapy is not appropriate under any circumstances.

Summary Statement 63: If a patient on immunotherapy transfers from one physician to another, a decision must be made by the physician to whom the patient has transferred

as to whether to continue immunotherapy. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program from one physician to another. In addition, a record of previous response to and compliance with this program should be communicated to the patient's new physician. **D**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often transfer from one physician (previous physician) to another (current physician) while receiving allergen immunotherapy. When this occurs, a decision must be made by the current physician about whether to continue immunotherapy and, if so, what allergen immunotherapy extract and schedule should be used: the one that the patient brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

If the patient transfers from one physician to another and continues on the previous immunotherapy program without changing either the schedule or allergen immunotherapy extract, he or she is not at substantially increased risk of having systemic reactions as long as there is a full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program must accompany the patient who transfers responsibility for the immunotherapy program from one physician to another. This should include a record of any reactions to immunotherapy and how they were managed, as well as the patient's response to immunotherapy. Under these circumstances, immunotherapy can be continued with the allergen immunotherapy extract that the patient was previously receiving if (1) the previous physician is willing and able to continue to provide the patient with a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the allergen immunotherapy extract. These include changes in the lot, manufacturer, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens and started on an immunotherapy schedule and immunotherapy extract formulation that is appropriate. In this situation the starting dose should be comparable with the initial dose that would be used if the patient had not previously been receiving immunotherapy. If the information that accompanies the patient is thorough, the current physician can prepare an allergen immunotherapy extract identical or almost identical to that provided by the previous physician. In such a case, all that might be required is a decrease in the dose from the patient's previous injection provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] However, this study did not include an important allergen, cockroach, which has been shown to correlate with asthma severity in other studies of inner-city asthmatic children.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is difficulty in communicating with the child regarding systemic reactions, and (2) injections can be traumatic to very young children. Therefore each case should be considered individually by weighing the benefits and risks. For children who have had a history of anaphylaxis to stinging insects or have severe allergic disease, the benefits of allergen immunotherapy might outweigh the risks.

Immunotherapy in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). The initiation of immunotherapy might be considered during pregnancy when the clinical indication for immunotherapy is a high-risk medical condition, such as anaphylaxis caused by Hymenoptera hypersensitivity. When a patient receiving immunotherapy reports that she is pregnant, the dose of immunotherapy is usually not increased, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older patients might be taking medications that could make treatment of anaphylaxis with epinephrine more difficult, such as β-blockers, or might have significant comorbid medical conditions, such as hypertension, coronary artery disease, cerebrovascular disease, and/or cardiac arrhythmias. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

Although concern about the safety of allergen immunotherapy in patients with autoimmune disease or connective tissue disease has been raised in the past, there is no substantive evidence that such treatment is harmful in these diseases. Therefore the benefits and risks of allergen immunotherapy in patients with autoimmune or connective tissue must be assessed on an individual basis.

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]

FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

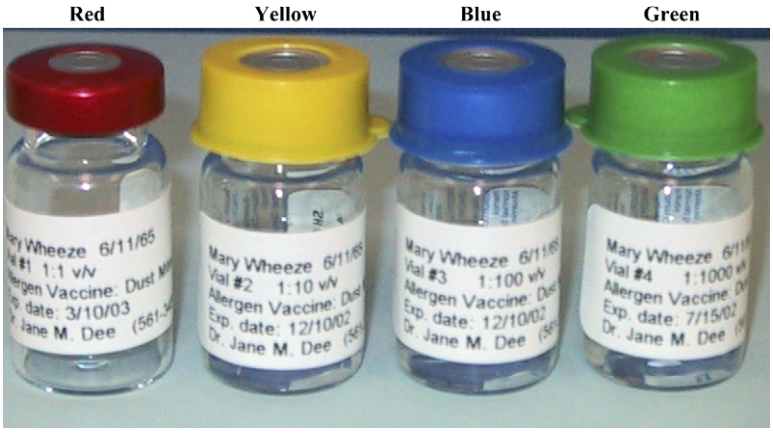


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S NOTE

Examples of allergen immunotherapy prescription and administration forms, immunotherapy labels, conventional and cluster build-up schedules, immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals, summaries of documentation guidelines, systemic reaction reporting sheets, and 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

REFERENCES

1. American College of Medical Quality's policy on development and use of practice parameters for medical quality decision-making. Available at: http://www.acmq.orq/profess/PDFs/policy5.pdf. Accessed September 26, 2006.
2. American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter. Ann Allergy Asthma Immunol 2003; 90(suppl 1):1-40.
3. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.
4. Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol 2004;113:1117-21. **III**
5. Joint Commission National Patient Safety Goals. Available at: http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/. Accessed December 26, 2006.
6. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. 2006:855-9. **III**
7. Polosa R, Li Gotti F, Mangano G, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. Allergy 2004;59:1224-8. **III**
8. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. Respir Res 2005; 6:153. **III**
9. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6. **Ib**
10. Williams PB, Ahlstedt S, Barnes JH, Soderstrom L, Portnoy J. Are our impressions of allergy test performances correct? Ann Allergy Asthma Immunol 2003;91:26-33.
11. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2005;115:584-91.
12. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl 2):S483-523.
13. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75. **Ib**
14. Des Roches A, Paradis L, Knani J, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. Allergy 1996;51:430-3. **III**
15. Kao N. Terminology used for allergen immunotherapy. Ann Allergy Asthma Immunol 2000;84:273-4.
16. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy 2006;61(suppl 82):1-20.
17. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Geneva: January 27-29 1997. Allergy 1998;53(suppl):1-42.
18. Nicklas RA, Bernstein IL, Blessing-Moore J, et al. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
19. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;1: 1572-3.
20. Freeman J. Further observations of the treatment of hay fever by hypodermic inoculations of pollen vaccine. Lancet 1911;2:814-7.
21. Freeman J. "Rush Inoculation," with special reference to hay fever treatment. Lancet 1930;1:744-7.
22. Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. J Allergy Clin Immunol 2003;111: 155-61. **Ib**
23. Creticos PS, Van Metre TE, Mardiney MR, Rosenberg GL, Norman PS, Adkinson NF Jr. Dose response of IgE and IgG antibodies during ragweed immunotherapy. J Allergy Clin Immunol 1984;73: 94-104. **Ib**
24. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117: 319-25. **Ib**
25. Lent AM, Harbeck R, Strand M, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. J Allergy Clin Immunol 2006;118:1249-56.
26. Nanda A, O'Connor M, Anand M, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J Allergy Clin Immunol 2004;114:1339-44. **Ib**
27. Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;66:500-13. **III**
28. Van Metre TE, Adkinson NF, Lichtenstein LM, et al. A controlled study of the effectiveness of the Rinkel method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;65: 288-97. **III**
29. Till SJ, Durham SR. Immunological responses to allergen immunotherapy. Clin Allergy Immunol 2004;18:85-104.
30. Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004;113:1025-35.
31. Durham SR, Ying S, Varney VA, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells

expressing messenger RNA for interferon-gamma. J Allergy Clin Immunol 1996;97:1356-65. **Ib**

32. Evans R, Pence H, Kaplan H, Rocklin RE. The effect of immunotherapy on humoral and cellular responses in ragweed hayfever. J Clin Invest 1976;57:1378-85. **IIa**
33. Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. J Allergy Clin Immunol 1997;99:254-60. **IIb**
34. Tulic MK, Fiset PO, Christodoulopoulos P, et al. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. J Allergy Clin Immunol 2004;113: 235-41. **Ib**
35. Bellinghausen I, Metz G, Enk AH, Christmann S, Knop J, Saloga J. Insect venom immunotherapy induces interleukin-10 production and a Th2-to-Th1 shift, and changes surface marker expression in venom-allergic subjects. Eur J Immunol 1997;27:1131-9. **LB**
36. Blaser K, Akdis CA. Interleukin-10, T regulatory cells and specific allergy treatment. Clin Exp Allergy 2004;34:328-31.
37. Francis JN, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. J Allergy Clin Immunol 2003; 111:1255-61. **LB**
38. Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol 2003;33:1205-14. **IIb**
39. Savolainen J, Laaksonen K, Rantio-Lehtimaki A, Terho EO. Increased expression of allergen-induced in vitro interleukin-10 and interleukin-18 mRNA in peripheral blood mononuclear cells of allergic rhinitis patients after specific immunotherapy. Clin Exp Allergy 2004;34:413-9. **IIa**
40. Durham SR, Varney VA, Gaga M, et al. Grass pollen immunotherapy decreases the number of mast cells in the skin. Clin Exp Allergy 1999; 29:1490-6. **Ib**
41. Moingeon P, Batard T, Fadel R, Frati F, Sieber J, Overtvelt L. Immune mechanisms of allergen-specific sublingual immunotherapy. Allergy 2006;61:151-65.
42. Bousquet J, Braquemond P, Feinberg J, Guerin B, Maasch H, Michel FB. Specific IgE response before and after rush immunotherapy with a standardized allergen or allergoid in grass pollen allergy. Ann Allergy 1986;56:456-9. **LB**
43. Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol 1982;70:261-71. **IIa**
44. Lichtenstein LM, Ishizaka K, Norman PS, Sobotka AK, Hill BM. IgE antibody measurements in ragweed hay fever. Relationship to clinical severity and the results of immunotherapy. J Clin Invest 1973;52: 472-82. **IIb**
45. Creticos P, Adkinson NF Jr, Kagey-Sobotka A, et al. Nasal challenge with ragweed pollen in hay fever patients: effect of immunotherapy. J Clin Invest 1985;76:2247-53. **IIb**
46. Rak S, Lowhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. J Allergy Clin Immunol 1988;82:470-80. **IIb**
47. Sadan N, Rhyne MB, Mellitis ED, Goldstein EO, Levy DA, Lichtenstein LM. Immunotherapy of pollinosis in children. Investigation of the immunologic basis of clinical improvement. N Engl Med 1969; 280:623-7. **IIa**
48. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. J Clin Invest 1993;92: 644-51. **IIb**
49. Ewan PW, Deighton J, Wilson AB, Lachmann PJ. Venom-specific IgG antibodies in bee and wasp allergy: lack of correlation with protection from stings. Clin Exp Allergy 1993;23:647-60. **IIb**
50. Djurup R, Malling HJ. High IgG4 antibody level is associated with failure of immunotherapy with inhalant allergens. Clin Allergy 1987;17: 459-68. **IIb**
51. Michils A, Baldassarre S, Ledent C, Mairesse M, Gossart B, Duchateau J. Early effect of ultrarush venom immunotherapy on the IgG antibody response. Allergy 2000;55:455-62. **IIb**
52. Michils A, Mairesse M, Ledent C, Gossart B, Baldassarre S, Duchateau J. Modified antigenic reactivity of anti-phospholipase A2 IgG antibodies in patients allergic to bee venom: conversion with immunotherapy and relation to subclass expression. J Allergy Clin Immunol 1998;102:118-26. **IIb**
53. Wachholz PA, Soni NK, Till SJ, Durham SR. Inhibition of allergen-IgE binding to B cells by IgG antibodies after grass pollen immunotherapy. J Allergy Clin Immunol 2003;112:915-22. **Ib**
54. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998;102:558-62.
55. American Academy of Allergy, Asthma and Immunology (AAAAI). The use of standardized allergen extracts. J Allergy Clin Immunol 1997;99:583-6.
56. Nelson HS. The use of standardized extracts in allergen immunotherapy. J Allergy Clin Immunol 2000;106:41-5.
57. Turkeltaub P. Allergenic extracts. II. In vivo standardization. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, editors. Allergy: principles and practice. 3rd ed. St Louis: CV Mosby; 1988. p. 388-401.
58. Lombardero M, Carreira J, Duffort O. Monoclonal antibody based radioimmunoassay for the quantitation of the main cat allergen (Fel d I or Cat-1). J Immunol Methods 1988;108:71-6. **LB**
59. Ohman JL Jr, Sundin B. Standardized allergenic extracts derived from mammals. Clin Rev Allergy 1987;5:37-47.
60. Lockey R, Slater J, Esch E. Preparation of standardization of allergen extracts. In: Adkinson F, Yunginger J, Busse W, Bochner B, Holgate S, Simons E, editors. Middleton's allergy: principles and practice. 6th ed. St Louis: Mosby; 2003. p. 573-84.
61. Cabanas R, Lopez-Serrano MC, Carreira J, et al. Importance of albumin in cross-reactivity among cat, dog and horse allergens. J Investig Allergol Clin Immunol 2000;10:71-7. **LB**
62. Baer H, Godfrey H, Maloney CJ, Norman PS, Lichtenstein LM. The potency and antigen E content of commercially prepared ragweed extracts. J Allergy 1970;45:347-54. **IIb**
63. Baer H, Maloney CJ, Norman PS, Marsh DG. The potency and group I antigen content of six commercially prepared grass pollen extracts. J Allergy Clin Immunol 1974;54:157-64. **IIb**
64. Greenert S, Bernstein IL, Michael JG. Immune responses of non-atopic individuals to prolonged immunisation with ragweed extract. Lancet 1971;2:1121-3. **IIb**
65. Modrzynski M, Zawisza E, Moverare R, et al. Development of new IgE specificities to allergenic components in birch pollen extract during specific immunotherapy studied with immunoblotting and Pharmacia CAP System. Przegl Lek 2003;60:130-2. **IIa**
66. Moverare R, Elfman L, Vesterinen E, Metso T, Haahtela T. Development of new IgE specificities to allergenic components in birch pollen extract during specific immunotherapy studied with immunoblotting and Pharmacia CAP System. Allergy 2002;57:423-30. **IIa**
67. Leiferman KM, Gleich GJ. The cross-reactivity of IgE antibodies with pollen allergens. I. Analyses of various species of grass pollens. J Allergy Clin Immunol 1976;58(suppl):129-39. **LB**
68. Fahlbusch B, Muller WD, Rudeschko O, Jager L, Cromwell O, Fiebig H. Detection and quantification of group 4 allergens in grass pollen extracts using monoclonal antibodies. Clin Exp Allergy 1998;28:799-807. **LB**
69. Gonzalez RM, Cortes C, Conde J, et al. Cross-reactivity among five major pollen allergens. Ann Allergy 1987;59:149-54. **LB**
70. Karl S, Rakoski J. Hyposensitization with cross-reacting pollen allergens. Z Hautkr 1988;63(suppl 4):55-7. **LB**
71. Leavengood DC, Renard RL, Martin BG, Nelson HS. Cross allergenicity among grasses determined by tissue threshold changes. J Allergy Clin Immunol 1985;76:789-94. **III**
72. Lowenstein H. Timothy pollen allergens. Allergy 1980;35:188-91. **LB**
73. Martin BG, Mansfield LE, Nelson HS. Cross-allergenicity among the grasses. Ann Allergy 1985;54:99-104. **LB**
74. van Ree R, van Leeuwen WA, Aalberse RC. How far can we simplify in vitro diagnostics for grass pollen allergy?: a study with 17 whole pollen extracts and purified natural and recombinant major allergens. J Allergy Clin Immunol 1998;102:184-90. **LB**
75. Bernstein IL, Perera M, Gallagher J, Michael JG, Johansson SG. In vitro cross-allergenicity of major aeroallergenic pollens by the radioallergosorbent technique. J Allergy Clin Immunol 1976;57: 141-52. **LB**

76. Phillips JW, Bucholtz GA, Fernandez-Caldas E, Bukantz SC, Lockey RF. Bahia grass pollen, a significant aeroallergen: evidence for the lack of clinical cross-reactivity with timothy grass pollen. Ann Allergy 1989;63:503-7. **IIa**
77. Eusebius NP, Papalia L, Suphioglu C, et al. Oligoclonal analysis of the atopic T cell response to the group 1 allergen of *Cynodon dactylon* (Bermuda grass) pollen: pre- and post-allergen-specific immunotherapy. Int Arch Allergy Immunol 2002;127:234-44. **LB**
78. Blaher B, Suphioglu C, Knox RB, Singh MB, McCluskey J, Rolland JM. Identification of T-cell epitopes of Lol p 9, a major allergen of ryegrass *(Lolium perenne)* pollen. J Allergy Clin Immunol 1996;98: 124-32. **LB**
79. Barletta B, Afferni C, Tinghino R, Mari A, Di Felice G, Pini C. Cross-reactivity between *Cupressus arizonica* and *Cupressus sempervirens* pollen extracts. J Allergy Clin Immunol 1996;98:797-804. **LB**
80. Black J. Cedar hay fever. J Allergy 1929;1:71-3. **III**
81. Pham NH, Baldo BA, Bass DJ. Cypress pollen allergy. Identification of allergens and crossreactivity between divergent species. Clin Exp Allergy 1994;24:558-65. **LB**
82. Yoo TJ, Spitz E, McGerity JL. Conifer pollen allergy: studies of immunogenicity and cross antigenicity of conifer pollens in rabbit and man. Ann Allergy 1975;34:87-93. **III**
83. Lowenstein H. Cross reactions among pollen antigens. Allergy 1980; 35:198-200. **LB**
84. Weber RW. Cross-reactivity of pollen allergens. Curr Allergy Asthma Rep 2004;4:401-8. **III**
85. Zetterstrom O, Fagerberg E, Wide L. An investigation of pollen extracts from different deciduous trees in patients with springtime allergy in Sweden. Acta Allergol 1972;27:15-21. **III**
86. Eriksson NE, Wihl JA, Arrendal H, Strandhede SO. Tree pollen allergy. III. Cross reactions based on results from skin prick tests and the RAST in hay fever patients. A multi-centre study. Allergy 1987;42:205-14. **LB**
87. Niederberger V, Pauli G, Gronlund H, et al. Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations. J Allergy Clin Immunol 1998;102:579-91. **LB**
88. White JF, Bernstein DI. Key pollen allergens in North America. Ann Allergy Asthma Immunol 2003;91:425-36, 92.
89. Bousquet J, Guerin B, Hewitt B, Lim S, Michel FB. Allergy in the Mediterranean area. III: cross reactivity among *Oleaceae* pollens. Clin Allergy 1985;15:439-48. **LB**
90. Kernerman SM, McCullough J, Green J, Ownby DR. Evidence of cross-reactivity between olive, ash, privet, and Russian olive tree pollen allergens. Ann Allergy 1992;69:493-6. **III**
91. Leiferman KM, Gleich GJ, Jones RT. The cross-reactivity of IgE antibodies with pollen allergens. II. Analyses of various species of ragweed and other fall weed pollens. J Allergy Clin Immunol 1976;58(suppl): 140-8. **LB**
92. Yunginger JW, Gleich GJ. Measurement of ragweed antigen E by double antibody radioimmunoassay. J Allergy Clin Immunol 1972;50: 326-37. **LB**
93. Asero R, Weber B, Mistrello G, Amato S, Madonini E, Cromwell O. Giant ragweed specific immunotherapy is not effective in a proportion of patients sensitized to short ragweed: analysis of the allergenic differences between short and giant ragweed. J Allergy Clin Immunol 2005; 116:1036-41. **IIa**
94. Katial RK, Lin FL, Stafford WW, Ledoux RA, Westley CR, Weber RW. Mugwort and sage *(Artemisia)* pollen cross-reactivity: ELISA inhibition and immunoblot evaluation. Ann Allergy Asthma Immunol 1997;79:340-6. **LB**
95. Lewis W, Vinay P, Zenger VE. Airborne and allergenic pollen of North America. Baltimore (MD): The John Hopkins University Press; 1983.
96. Barderas R, Villalba M, Lombardero M, Rodriguez R. Identification and characterization of Che a 1 allergen from *Chenopodium album* pollen. Int Arch Allergy Immunol 2002;127:47-54. **LB**
97. Gomez J, Mansfield LE, Frederick RW, Rael ED. Analysis of the individual allergens of Russian thistle pollen by an enzyme-linked immunoblotting technique. J Asthma 1989;26:243-50. **LB**
98. Shafiee A, Yunginger JW, Gleich GJ. Isolation and characterization of Russian thistle *(Salsola pestifer)* pollen allergens. J Allergy Clin Immunol 1981;67:472-81. **LB**
99. Weber RW, Nelson HS. Pollen allergens and their interrelationships. Clin Rev Allergy 1985;3:291-318. **III**
100. Weber RW NH. Chenopod-Amaranth cross-allergenicity: evaluated by RAST inhibition. Ann Allergy 1984;52:226. **LB**
101. Weber R. Cross-reactivity among Chenopod-Amaranth weeds: skin test correlation. Ann Allergy 1987;58:287. **LB**
102. Helm RM, Squillace DL, Jones RT, Brenner RJ. Shared allergenic activity in Asian *(Blattella asahinai)*, German *(Blattella germanica)*, American *(Periplaneta americana)*, and Oriental *(Blatta orientalis)* cockroach species. Int Arch Allergy Appl Immunol 1990;92:154-61. **LB**
103. Jeong KY, Lee J, Lee IY, Ree HI, Hong CS, Yong TS. Allergenicity of recombinant Bla g 7, German cockroach tropomyosin. Allergy 2003;58: 1059-63. **LB**
104. Abramson MJ, Puy MR, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151:969-74. **Ia**
105. Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American Academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81:401-5.
106. Lockey RF. "ARIA": global guidelines and new forms of allergen immunotherapy. J Allergy Clin Immunol 2001;108:497-9.
107. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis. Clin Ther 2000;22: 342-50. **Ia**
108. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: a meta-analysis. Clin Ther 2000;22:351-8. **Ia**
109. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. Clin Ther 2000;22: 329-41. **Ia**
110. Portnoy JM. Immunotherapy for asthma: unfavorable studies. Ann Allergy Asthma Immunol 2001;87(suppl 1):28-32.
111. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. Cochrane Database Syst Rev 2003:CD001186. **Ia**
112. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N Engl J Med 1965;273:675-9. **Ib**
113. Pichler CE, Helbling A, Pichler WJ. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. Allergy 2001;56: 301-6. **IIb**
114. Aas K. Hyposensitization in house dust allergy asthma. A double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. Acta Paediatr Scand 1971;60:264-8. **Ib**
115. Bonno M, Fujisawa T, Iguchi K, et al. Mite-specific induction of interleukin-2 receptor on T lymphocytes from children with mite-sensitive asthma: modified immune response with immunotherapy. J Allergy Clin Immunol 1996;97:680-8. **IIa**
116. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med 1978;299:157-61. **IIa**
117. Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 1997;7:90-7. **IIa**
118. Cantani A, Micera M. Is specific immunotherapy safe and effective in children? Eur Rev Med Pharmacol Sci 2000;4:139-43. **IV**
119. Cools M, Van Bever HP, Weyler JJ, Stevens WJ. Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. Allergy 2000;55:69-73. **IIa**
120. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3. **III**
121. Hedlin G, Wille S, Browaldh L, et al. Immunotherapy in children with allergic asthma: Effect on bronchial hyperreactivity and pharmacotherapy. J Allergy Clin Immunol 1999;103:609-14. **Ib**

122. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14-year study. Pediatrics 1968;42: 793-802. **Ib**
123. Ohashi Y, Nakai Y, Tanaka A, et al. Serologic study of the working mechanisms of immunotherapy for children with perennial allergic rhinitis. Arch Otolaryngol Head Neck Surg 1998;124:1337-46. **III**
124. Portnoy JM. Immunotherapy for allergic diseases. Clin Rev Allergy Immunol 2001;21:241-59.
125. Ariano R, Kroon AM, Augeri G, Canonica GW, Passalacqua G. Long-term treatment with allergoid immunotherapy with *Parietaria*. Clinical and immunologic effects in a randomized, controlled trial. Allergy 1999;54:313-9. **Ib**
126. Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. J Allergy Clin Immunol 1991;88:43-53. **Ib**
127. Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 1987;80:591-8. **Ib**
128. Creticos PS, Marsh DG, Proud D, et al. Responses to ragweed-pollen nasal challenge before and after immunotherapy. J Allergy Clin Immunol 1989;84:197-205. **Ib**
129. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334:501-6. **Ib**
130. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy 1996;51:489-500. **Ib**
131. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. JAMA 1967;201:951-7.
132. Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria judaica* in patients with *Parietaria* hay fever. Allergy 1994;49:13-21. **Ib**
133. Malling HJ, Djurup R. Diagnosis and immunotherapy of mould allergy. VII. IgG subclass response and relation to the clinical efficacy of immunotherapy with *Cladosporium*. Allergy 1988;43:60-70.
134. Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. J Allergy Clin Immunol 1990;85:460-72. **IIa**
135. Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with *Cladosporium herbarum*. Allergy 1986;41:507-19. **Ib**
136. Malling HJ. Diagnosis and immunotherapy of mould allergy. IV. Relation between asthma symptoms, spore counts and diagnostic tests. Allergy 1986;41:342-50. **IIa**
137. Karlsson R, Agrell B, Dreborg S, et al. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation. II. In vitro results. Allergy 1986;41:141-50. **Ib**
138. Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. I. Clinical results. Allergy 1986;41:131-40. **Ib**
139. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quiros A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol 1994;93:556-66. **Ib**
140. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander. I. Clinical results. Allergy 1992;47:249-54. **IIa**
141. Hedlin G, Graff-Lonnevig V, Heilborn H, et al. Immunotherapy with cat- and dog-dander extracts. V. Effects of 3 years of treatment. J Allergy Clin Immunol 1991;87:955-64. **IIa**
142. Ohman JL Jr, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma. Double-blind trial with evaluation of in vivo and in vitro responses. J Allergy Clin Immunol 1984;74:230-9. **Ib**
143. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. Clin Exp Allergy 1997;27:860-7. **Ib**
144. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol 2004;113:643-9. **Ib**
145. Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. J Allergy Clin Immunol 2005;116:109-18. **Ib**
146. Pichler CE, Marquardsen A, Sparholt S, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D. farinae* results in decreased bronchial hyperreactivity. Allergy 1997;52:274-83. **Ib**
147. Bousquet J, Calvayrac P, Guerin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of treatment. J Allergy Clin Immunol 1985;76:734-44. **Ib**
148. Bousquet J, Hejjaoui A, Clauzel AM, et al. Specific immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. II. Prediction of efficacy of immunotherapy. J Allergy Clin Immunol 1988;82:971-7. **IIa**
149. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol 1993;91:709-22. **Ib**
150. McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of *Dermatophagoides pteronyssinus* in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol 1990;86:521-31. **Ib**
151. Olsen OT, Larsen KR, Jacobsan L, Svendsen UG. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. Allergy 1997;52:853-9. **Ib**
152. Pauli G, Bessot JC, Bigot H, et al. Clinical and immunologic evaluation of tyrosine-adsorbed *Dermatophagoides pteronyssinus* extract: a double-blind placebo-controlled trial. J Allergy Clin Immunol 1984;74:524-35. **Ib**
153. Wang H, Lin X, Hao C, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy 2006;61:191-7. **Ib**
154. Kang BC, Johnson J, Morgan C, Chang JL. The role of immunotherapy in cockroach asthma. J Asthma 1988;25:205-18. **IB**
155. Freeman TM, Hylander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. J Allergy Clin Immunol 1992;90:210-5. **IIa**
156. Triplett RF. Sensitivity to the imported fire ant: successful treatment with immunotherapy. South Med J 1973;66:477-80. **III**
157. Tankersley MS, Walker RL, Butler WK, Hagan LL, Napoli DC, Freeman TM. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. J Allergy Clin Immunol 2002;109:556-62. **Ib**
158. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy 2005;60:801-7. **Ib**
159. Ferrer M, Burches E, Pelaez A, et al. Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: clinical efficacy and tolerance. J Investig Allergol Clin Immunol 2005;15:283-92. **Ib**
160. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 2005;116:608-13. **Ib**
161. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001;107:87-93. **Ib**
162. Jacobsen L, Nuchel Petersen B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. Allergy 1997;52:914-20. **III**
163. Eng PA, Borer-Reinhold M, Heijnen IAFM, Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61:198-201. **IIa**
164. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002;57:306-12. **IIa**
165. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. Ann Allergy Asthma Immunol 2001; 87(suppl 1):43-6. **IV**
166. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31:1392-7. **IIa**

167. Purello-D'Ambrosio F, Gangemi S, Merendino RA, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001;31:1295-302.
168. Sampson HA. Food anaphylaxis. Br Med Bull 2000;56:925-35.
169. Rance F. [Current childhood food allergies]. Allerg Immunol (Paris) 2000;32:366-76. **IIb**
170. Bannon GA, Cockrell G, Connaughton C, et al. Engineering, characterization and in vitro efficacy of the major peanut allergens for use in immunotherapy. Int Arch Allergy Immunol 2001;124:70-2. **LB**
171. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 1997;99:744-51. **IIa**
172. Enrique E, Pineda F, Malek T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol 2005;116:1073-9. **Ib**
173. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992;90:256-62. **Ib**
174. Werfel T, Breuer K, Rueff F, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. Allergy 2006;61:202-5. **Ib**
175. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. Clin Exp Allergy 1992;22:440-6. **Ib**
176. Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? J Allergy Clin Immunol 2006;118:1292-8.
177. Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004;59:1272-6. **IIa**
178. Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. Mol Nutr Food Res 2004;48:441-8. **Ib**
179. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. J Allergy Clin Immunol 2000;106:840-3. **III**
180. Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. Ann Allergy Asthma Immunol 2004;92:225-7. **III**
181. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions in patients who experience systemic reactions on allergen immunotherapy. Ann Allergy Asthma Immunol 2007;99:82-6. **III**
182. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87(suppl 1):47-55. **III**
183. Malling HJ. Minimising the risks of allergen-specific injection immunotherapy. Drug Saf 2000;23:323-32.
184. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006;117:169-75. **III**
185. Ragusa FV, Passalacqua G, Gambardella R, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 1997;7:151-4. **III**
186. Ragusa VF, Massolo A. Non-fatal systemic reactions to subcutaneous immunotherapy: a 20-year experience comparison of two 10-year periods. Allerg Immunol (Paris) 2004;36:52-5. **III**
187. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy 2004;34:527-31. **III**
188. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;113:1129-36. **III**
189. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79:660-77. **III**
190. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993;92:6-15. **III**
191. Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 1989;83:797-802. **IIa**
192. Greenberg MA, Kaufman CR, Gonzalez GE, Rosenblatt CD, Smith LJ, Summers RJ. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986;77:865-70.
193. Matloff SM, Bailit IW, Parks P, Madden N, Greineder DK. Systemic reactions to immunotherapy. Allergy Proc 1993;14:347-50. **IV**
194. Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.
195. Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F. Refractory anaphylactoid shock potentiated by beta-blockers. Catheter Cardiovasc Diagn 1996;39:383-4.
196. Kivity S, Yarchovsky J. Relapsing anaphylaxis to bee sting in a patient treated with beta-blocker and Ca blocker. J Allergy Clin Immunol 1990;85:669-70. **IV**
197. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. Arch Intern Med 1993;153:2033-40. **III**
198. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. Ann Intern Med 1991;115:270-6. **III**
199. Bickell WH, Dice WH. Military antishock trousers in a patient with adrenergic-resistant anaphylaxis. Ann Emerg Med 1984;13:189-90. **IV**
200. Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981;68:125-7. **IV**
201. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. Ann Allergy 1981;47:35-7. **IV**
202. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 1988;81:1-5. **IV**
203. Hepner MJ, Ownby DR, Anderson JA, Rowe MS, Sears-Ewald D, Brown EB. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. J Allergy Clin Immunol 1990;86:407-11. **III**
204. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. J Allergy Clin Immunol 2005;115:606-10. **III**
205. Sherman MS, Lazar EJ, Eichacker P. A bronchodilator action of glucagon. J Allergy Clin Immunol 1988;81:908-11. **IV**
206. Thomas M, Crawford I. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. Emerg Med J 2005;22:272-3. **IV**
207. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000;30:1144-50. **III**
208. Simons FE, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? J Allergy Clin Immunol 2001;108:1040-4. **IIa**
209. Simons FE, Gu X, Johnston LM, Simons KJ. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? Pediatrics 2000;106:1040-4. **Ib**
210. Simons FE, Gu X, Silver NA, Simons KJ. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. J Allergy Clin Immunol 2002;109:171-5. **Ib**
211. Simons FE, Gu X, Simons KJ. Outdated EpiPen and EpiPen Jr autoinjectors: past their prime? J Allergy Clin Immunol 2000;105:1025-30. **Ib**
212. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001;108:871-3. **Ib**
213. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998;101:33-7. **Ib**
214. Bernstein JA. Pharmacoeconomic considerations for allergen immunotherapy. Clin Allergy Immunol 2004;18:151-64. **III**
215. Practice parameters for the diagnosis and treatment of asthma. Joint Task Force on Practice Parameters, representing the American Academy of Allergy Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy,

Asthma and Immunology. J Allergy Clin Immunol 1995;96(suppl): S707-870.
216. Li JT, Pearlman DS, Nicklas RA, et al. Algorithm for the diagnosis and management of asthma: a practice parameter update: Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81:415-20.
217. Current status of allergen immunotherapy: Shortened Version of a World Health Organisation/International Union of Immunological Societies Working Group Report. Lancet 1989;333:259-61.
218. Moffitt JE, Golden DB, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114: 869-86.
219. Duplantier JE, Freeman TM, Bahna SL, Good RA, Sher MR. Successful rush immunotherapy for anaphylaxis to imported fire ants. J Allergy Clin Immunol 1998;101:855-6. **IV**
220. Nguyen SA, Napoli DC. Natural history of large local and generalized cutaneous reactions to imported fire ant stings in children. Ann Allergy Asthma Immunol 2005;94:387-90. **III**
221. Valentine MD, Schuberth KC, Kagey-Sobotka A, et al. The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med 1990;323:1601-3. **III**
222. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med 2004;351:668-74. **III**
223. Golden DB, Marsh DG, Kagey-Sobotka A, et al. Epidemiology of insect venom sensitivity. JAMA 1989;262:240-4. **III**
224. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. J Allergy Clin Immunol 2005;115:439-48. **IV**
225. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Insect sting allergy with negative venom skin test responses. J Allergy Clin Immunol 2001;107:897-901. **IIa**
226. Golden DB, Tracy JM, Freeman TM, Hoffman DR. Negative venom skin test results in patients with histories of systemic reaction to a sting. J Allergy Clin Immunol 2003;112:495-8. **IV**
227. Reisman RE. Insect sting allergy: the dilemma of the negative skin test reactor. J Allergy Clin Immunol 2001;107:781-2. **IV**
228. Arbes SJ Jr, Cohn RD, Yin M, Muilenberg ML, Friedman W, Zeldin DC. Dog allergen (Can f 1) and cat allergen (Fel d 1) in US homes: results from the National Survey of Lead and Allergens in Housing. J Allergy Clin Immunol 2004;114:111-7. **III**
229. Matsui EC, Wood RA, Rand C, Kanchanaraksa S, Swartz L, Eggleston PA. Mouse allergen exposure and mouse skin test sensitivity in suburban, middle-class children with asthma. J Allergy Clin Immunol 2004; 113:910-5. **III**
230. Matsui EC, Simons E, Rand C, et al. Airborne mouse allergen in the homes of inner-city children with asthma. J Allergy Clin Immunol 2005;115:358-63. **III**
231. Perry T, Matsui E, Merriman B, Duong T, Eggleston P. The prevalence of rat allergen in inner-city homes and its relationship to sensitization and asthma morbidity. J Allergy Clin Immunol 2003;112:346-52. **III**
232. Lin MS, Tanner E, Lynn J, Friday GA Jr. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. Ann Allergy 1993; 71:557-62. **III**
233. Valyasevi MA, Maddox DE, Li JT. Systemic reactions to allergy skin tests. Ann Allergy Asthma Immunol 1999;83:132-6. **III**
234. Berg TL, Johansson SG. Allergy diagnosis with the radioallergosorbent test: a comparison with the results of skin and provocation tests in an unselected group of children with asthma and hay fever. J Allergy Clin Immunol 1974;54:209-21. **IIb**
235. van der Zee JS, de Groot H, van Swieten P, Jansen HM, Aalberse RC. Discrepancies between the skin test and IgE antibody assays: study of histamine release, complement activation in vitro, and occurrence of allergen-specific IgG. J Allergy Clin Immunol 1988;82:270-81. **IIb**
236. Nelson HS, Oppenheimer J, Buchmeier A, Kordash TR, Freshwater LL. An assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to timothy grass. J Allergy Clin Immunol 1996;97:1193-201. **IIa**
237. Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. J Allergy Clin Immunol 1999;103:773-9. **IIa**
238. Esch RE. Manufacturing and standardizing fungal allergen products. J Allergy Clin Immunol 2004;113:210-5. **LB**
239. Vailes L, Sridhara S, Cromwell O, Weber B, Breitenbach M, Chapman M. Quantitation of the major fungal allergens, Alt a 1 and Asp f 1, in commercial allergenic products. J Allergy Clin Immunol 2001;107: 641-6. **LB**
240. Nelson HS, Ikle D, Buchmeier A. Studies of allergen extract stability: the effects of dilution and mixing. J Allergy Clin Immunol 1996;98: 382-8. **LB**
241. Salvaggio JE, Burge HA, Chapman JA. Emerging concepts in mold allergy: what is the role of immunotherapy? J Allergy Clin Immunol 1993;92:217-22.
242. Bertelsen A, Andersen JB, Christensen J, Ingemann L, Kristensen T, Ostergaard PA. Immunotherapy with dog and cat extracts in children. Allergy 1989;44:330-5. **Ib**
243. Schou C, Lind P, Fernandez-Caldas E, Lockey RF, Lowenstein H. Identification and purification of an important cross-reactive allergen from American *(Periplaneta americana)* and German *(Blattella germanica)* cockroach. J Allergy Clin Immunol 1990;86:935-46. **LB**
244. Bousquet J, Muller UR, Dreborg S, et al. Immunotherapy with Hymenoptera venoms. Position paper of the Working Group on Immunotherapy of the European Academy of Allergy and Clinical Immunology. Allergy 1987;42:401-13.
245. Rueff F, Wenderoth A, Przybilla B. Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses. J Allergy Clin Immunol 2001;108:1027-32. **III**
246. Kordash TR, Amend MJ, Williamson SL, Jones JK, Plunkett GA. Effect of mixing allergenic extracts containing helminthosporium, *D. farinae*, and cockroach with perennial ryegrass. Ann Allergy 1993;71:240-6. **LB**
247. Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability of standardized grass, dust mite, cat and short ragweed allergens after mixing with mold or cockroach extracts. Ann Allergy Asthma Immunol 2007;99:151-60. **LB**
248. Esch RE. Role of proteases on the stability of allergenic extracts. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 1992;85: 171-9. **LB**
249. Anderson MC, Baer H. Antigenic and allergenic changes during storage of a pollen extract. J Allergy Clin Immunol 1982;69:3-10. **LB**
250. Sridhara S, Singh BP, Arora N, Verma J, Gangal SV. A study on antigenic and allergenic changes during storage in three different biological extracts. Asian Pac J Allergy Immunol 1992;10:33-8. **LB**
251. Niemeijer NR, Kauffman HF, van Hove W, Dubois AE, de Monchy JG. Effect of dilution, temperature, and preservatives on the long-term stability of standardized inhalant allergen extracts. Ann Allergy Asthma Immunol 1996;76:535-40. **LB**
252. Vijay HM, Young NM, Bernstein IL. Studies on *Alternaria* allergens. VI. Stability of the allergen components of *Alternaria tenuis* extracts under a variety of storage conditions. Int Arch Allergy Appl Immunol 1987;83:325-8. **LB**
253. Ayuso R, Rubio M, Herrera T, Gurbindo C, Carreira J. Stability of *Lolium perenne* extract. Ann Allergy 1984;53:426-31. **LB**
254. Van Metre TE, Rosenberg GL, Vaswani SK, Ziegler SR, Adkinson NF. Pain and dermal reaction caused by injected glycerin in immunotherapy solutions. J Allergy Clin Immunol 1996;97:1033-9.
255. Lowenstein H. Domestic allergens. In: Kerr J, editor. Procedures of the XI International Congress of Allergology & Clinical Immunology. London: MacMillan; 1983. p. 545-8.
256. Lind P, Weeke B, Lowenstein H. A reference allergen preparation of the house dust mite *D. pteronyssinus*, produced from whole mite culture—a part of the DAS 76 study. Comparison with allergen preparations from other raw materials. Allergy 1984;39:259-74. **LB**
257. Lowenstein H, Marsh DG. Antigens of Ambrosia elatior (short ragweed) pollen. I. Crossed immunoelectrophoretic analyses. J Immunol 1981;126:943-8. **LB**
258. Lowenstein H, King TP, Goodfriend L, Hussain R, Roebber M, Marsh DG. Antigens of *Ambrosia elatior* (short ragweed) pollen. II. Immunochemical identification of known antigens by quantitative immunoelectrophoresis. J Immunol 1981;127:637-42. **LB**
259. Aukrust L. Crossed radioimmunoelectrophoretic studies of distinct allergens in two extracts of *Cladosporium herbarum*. Int Arch Allergy Appl Immunol 1979;58:375-90. **LB**

260. Bodtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy—a one-year, randomised, double-blind, placebo-controlled study. Allergy 2002;57:297-305. **Ib**
261. Pence HL, Mitchell DQ, Greely RL, Updegraff BR, Selfridge HA. Immunotherapy for mountain cedar pollinosis. A double-blind controlled study. J Allergy Clin Immunol 1976;58:39-50. **Ib**
262. Tipton WR, Nelson HS. Experience with daily immunotherapy in 59 adult allergic patients. J Allergy Clin Immunol 1982;69:194-9. **IIa**
263. Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol 2006;97:126-40. **202**
264. Mauro M, Russello M, Alesina R, et al. Safety and pharmacoeconomics of a cluster administration of mite immunotherapy compared to the traditional one. Allerg Immunol (Paris) 2006;38:31-4. **Ib**
265. Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. J Allergy Clin Immunol 1982;69:181-93. **Ib**
266. Tabar AI, Muro MD, Garcia BE, et al. *Dermatophagoides pteronyssinus* cluster immunotherapy. A controlled trial of safety and clinical efficacy. J Investig Allergol Clin Immunol 1999;9:155-64. **Ib**
267. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996;97: 1207-13. **Ib**
268. Miller DL, Mansmann HC Jr. Rapid injection therapy in children with intractable asthma: safety and technique. Ann Allergy 1971;29:178-86. **III**
269. Portnoy J, King K, Kanarek H, Horner S. Incidence of systemic reactions during rush immunotherapy. Ann Allergy 1992;68:493-8. **III**
270. Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80. **III**
271. Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. IV. Systemic reactions according to the immunotherapy schedule. J Allergy Clin Immunol 1990;85:473-9. **III**
272. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. Ann Allergy 1994;73:409-18. **Ib**
273. Harvey SM, Laurie S, Hilton K, Khan DA. Safety of rush immunotherapy to multiple aeroallergens in an adult population. Ann Allergy Asthma Immunol 2004;92:414-9. **III**
274. Roll A, Hofbauer G, Ballmer-Weber BK, Schmid-Grendelmeier P. Safety of specific immunotherapy using a four-hour ultra-rush induction scheme in bee and wasp allergy. J Investig Allergol Clin Immunol 2006;16:79-85. **III**
275. Jutel M, Skrbic D, Pichler WJ, Muller UR. Ultra rush bee venom immunotherapy does not reduce cutaneous weal responses to bee venom and codeine phosphate. Clin Exp Allergy 1995;25:1205-10. **III**
276. Bernstein JA, Kagen SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with Hymenoptera anaphylaxis. Ann Allergy 1994;73:423-8. **III**
277. Kohno Y, Minoguchi K, Oda N, et al. Effect of rush immunotherapy on airway inflammation and airway hyperresponsiveness after bronchoprovocation with allergen in asthma. J Allergy Clin Immunol 1998;102: 927-34. **IIa**
278. Schiavino D, Nucera E, Pollastrini E, et al. Specific ultrarush desensitization in Hymenoptera venom-allergic patients. Ann Allergy Asthma Immunol 2004;92:409-13. **III**
279. Goldberg A, Confino-Cohen R. Rush venom immunotherapy in patients experiencing recurrent systemic reactions to conventional venom immunotherapy. Ann Allergy Asthma Immunol 2003;91:405-10. **III**
280. Ohashi Y, Nakai Y, Murata K. Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2006;96:600-5. **Ib**
281. Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. J Allergy Clin Immunol 2001;107:81-6. **Ib**
282. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117:134-40. **Ib**
283. Golden DB, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol 2000; 105:385-90. **III**
284. The discontinuation of Hymenoptera venom immunotherapy. J Allergy Clin Immunol 1998;101:573-5. **IV**
285. Lerch E, Müller UR. Long-term protection after stopping venom immunotherapy: results of re-stings in 200 patients. J Allergy Clin Immunol 1998;101:606-12. **III**
286. van Halteren HK, van der Linden PW, Burgers JA, Bartelink AK. Discontinuation of yellow jacket venom immunotherapy: follow-up of 75 patients by means of deliberate sting challenge. J Allergy Clin Immunol 1997;100:767-70. **III**
287. Keating MU, Kagey-Sobotka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. J Allergy Clin Immunol 1991;88:339-48. **III**
288. Golden DB, Kwiterovich KA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. J Allergy Clin Immunol 1998;101:298-302. **III**
289. Wolf BL, Marks A, Fahrenholz JM. Accidental needle sticks, the Occupational Safety and Health Administration, and the fallacy of public policy. Ann Allergy Asthma Immunol 2006;97:52-4. **III**
290. Kanter L. Accidental needle stick prevention: an important, costly, unsafe policy revisited. Ann Allergy Asthma Immunol 2006;97:7-9. **IV**
291. Kanter LJ, Siegel C. Needle sticks and adverse outcomes in office-based allergy practices. Ann Allergy Asthma Immunol 2003;90:389-92. **III**
292. Position statement on the administration of immunotherapy outside of the prescribing allergist facility. Drugs and Anaphylaxis Committee of the American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81:101-2.
293. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336: 324-31. **Ib**
294. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997;336:1356-63. **III**
295. Asero R. Efficacy of injection immunotherapy with ragweed and birch pollen in elderly patients. Int Arch Allergy Immunol 2004;135:332-5.
296. Theodoropoulos DS, Lockey RF. Allergen immunotherapy: guidelines, update, and recommendations of the World Health Organization. Allergy Asthma Proc 2000;21:159-66.
297. Litwin A, Flanagan M, Entis G, et al. Oral immunotherapy with short ragweed extract in a novel encapsulated preparation: a double-blind study. J Allergy Clin Immunol 1997;100:30-8. **Ib**
298. Bjorksten B, Moller C, Broberger U, et al. Clinical and immunological effects of oral immunotherapy with a standardized birch pollen extract. Allergy 1986;41:290-5. **IIa**
299. Oppenheimer J, Areson JG, Nelson HS. Safety and efficacy of oral immunotherapy with standardized cat extract. J Allergy Clin Immunol 1994;93:61-7. **Ib**
300. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol 2006;97:141-8. **Ia**
301. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;118:434-40. **Ib**
302. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy 2005; 60:4-12. **Ia**
303. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:802-9.
304. Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. J Investig Allergol Clin Immunol 2005;15:9-16. **Ia**
305. Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. J Allergy Clin Immunol 1993;92:229-36. **Ib**
306. La Rosa M, Ranno C, Andre C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 1999;104: 425-32. **Ib**

307. Passalacqua G, Albano M, Riccio A, et al. Clinical and immunologic effects of a rush sublingual immunotherapy to *Parietaria* species: a double-blind, placebo-controlled trial. J Allergy Clin Immunol 1999; 104:964-8. **Ib**
308. Purello-D'Ambrosio F, Gangemi S, Isola S, et al. Sublingual immunotherapy: a double-blind, placebo-controlled trial with *Parietaria judaica* extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. Allergy 1999;54:968-73.
309. Sanchez Palacios A, Schamann F, Garcia JA. [Sublingual immunotherapy with cat epithelial extract. Personal experience]. Allergol Immunopathol (Madr) 2001;29:60-5. **Ib**
310. Andre C, Perrin-Fayolle M, Grosclaude M, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. Int Arch Allergy Immunol 2003;131: 111-8. **Ib**
311. Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. Allergy 2004;59:45-53. **Ib**
312. Bernardini R, Campodonico P, Burastero S, et al. Sublingual immunotherapy with a latex extract in paediatric patients: a double-blind, placebo-controlled study. Curr Med Res Opin 2006;22:1515-22. **Ib**
313. Cistero Bahima A, Sastre J, Enrique E, et al. Tolerance and effects on skin reactivity to latex of sublingual rush immunotherapy with a latex extract. J Investig Allergol Clin Immunol 2004;14:17-25. **Ib**
314. Marogna M, Spadolini I, Massolo A, et al. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. Ann Allergy Asthma Immunol 2007;98:274-80.
315. Bagnasco M, Mariani G, Passalacqua G, et al. Absorption and distribution kinetics of the major *Parietaria judaica* allergen (Par j 1) administered by noninjectable routes in healthy human beings. J Allergy Clin Immunol 1997;100:122-9. **IIb**
316. Passalacqua G, Altrinetti V, Mariani G, et al. Pharmacokinetics of radiolabelled Par j 1 administered intranasally to allergic and healthy subjects. Clin Exp Allergy 2005;35:880-3. **IIb**
317. Tripodi S, Di Rienzo Businco A, Benincori N, Scala G, Pingitore G. Safety and tolerability of ultra-rush induction, less than one hour, of sublingual immunotherapy in children. Int Arch Allergy Immunol 2006;139:149-52. **III**
318. Rossi RE, Monasterolo G. A pilot study of feasibility of ultra-rush (20-25 minutes) sublingual-swallow immunotherapy in 679 patients (699 sessions) with allergic rhinitis and/or asthma. Int J Immunopathol Pharmacol 2005;18:277-85. **III**
319. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 2006;61:185-90. **Ib**
320. Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. Allergy 2006;61:181-4. **Ib**
321. Marcucci F, Sensi L, Di Cara G, Incorvaia C, Frati F. Dose dependence of immunological response to sublingual immunotherapy. Allergy 2005;60:952-6. **Ib**
322. Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. J Allergy Clin Immunol 2006;117:1021-35. **Ia**
323. Bowen T, Greenbaum J, Charbonneau Y, et al. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. Ann Allergy Asthma Immunol 2004;93:425-30. **Ib**
324. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. Allergy 2005;60:133. **III**
325. Fiocchi A, Pajno G, La Grutta S, et al. Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. Ann Allergy Asthma Immunol 2005;95:254-8. **III**
326. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. Allergy 1999;54:1110-3. **III**
327. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. Allergy 2006;1236-7.
328. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. Allergy 2006;61:1235.
329. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy 2007;62: 567-8.
330. Georgitis JW, Clayton WF, Wypych JI, Barde SH, Reisman RE. Further evaluation of local intranasal immunotherapy with aqueous and allergoid grass extracts. J Allergy Clin Immunol 1984;74:694-700. **IIa**
331. Andri L, Senna G, Andri G, et al. Local nasal immunotherapy for birch allergic rhinitis with extract in powder form. Clin Exp Allergy 1995;25: 1092-9. **Ib**
332. Andri L, Senna GE, Betteli C, et al. Local nasal immunotherapy in allergic rhinitis to *Parietaria*. A double-blind controlled study. Allergy 1992;47:318-23. **Ib**
333. Passalacqua G, Albano M, Pronzato C, et al. Long-term follow-up of nasal immunotherapy to *Parietaria*: clinical and local immunological effects. Clin Exp Allergy 1997;27:904-8. **Ib**
334. Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to *Parietaria*: evidence of reduction of local allergic inflammation. Am J Respir Crit Care Med 1995;152:461-6. **IIa**
335. Andri L, Senna G, Betteli C, Givanni S, Andri G, Falagiani P. Local nasal immunotherapy for *Dermatophagoides*-induced rhinitis: efficacy of a powder extract. J Allergy Clin Immunol 1993;91:987-96. **Ib**
336. Radcliffe MJ, Lewith GT, Turner RG, Prescott P, Church MK, Holgate ST. Enzyme potentiated desensitisation in treatment of seasonal allergic rhinitis: double blind randomised controlled study. BMJ 2003;327:251-4. **Ib**
337. Ippoliti F, De Santis W, Volterrani A, et al. Immunomodulation during sublingual therapy in allergic children. Pediatr Allergy Immunol 2003; 14:216-21. **Ib**
338. Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. Clin Exp Allergy 2005;35:565-71. **III**
339. Smith H, White P, Annila I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. J Allergy Clin Immunol 2004;114:831-7. **Ib**
340. Norman PS, Ohman JL Jr, Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. Am J Respir Crit Care Med 1996;154:1623-8. **Ib**
341. Schramm G, Kahlert H, Suck R, et al. "Allergen engineering": variants of the timothy grass pollen allergen Phl p 5b with reduced IgE-binding capacity but conserved T cell reactivity. J Immunol 1999;162:2406-14. **LB**
342. Smith AM, Chapman MD, Taketomi EA, Platts-Mills TA, Sung SS. Recombinant allergens for immunotherapy: a Der p 2 variant with reduced IgE reactivity retains T-cell epitopes. J Allergy Clin Immunol 1998;101: 423-5. **LB**
343. Jain VV, Kitagaki K, Kline JN. CpG DNA and immunotherapy of allergic airway diseases. Clin Exp Allergy 2003;33:1330-5. **LB**
344. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med 2006;355:1445-55. **Ib**
345. Adelroth E, Rak S, Haahtela T, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2000;106:253-9. **Ib**
346. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics 2001; 108:E36. **Ib**
347. Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. N Engl J Med 1999;341:1966-73. **Ib**
348. Walker S, Monteil M, Phelan K, Lasserson T, Walters E. Anti-IgE for chronic asthma in adults and children. Cochrane Database Syst Rev 2006:CD003559. **Ia**
349. Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Allergy 1988;18:501-8.
350. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, Kagey-Sobotka A, Khattignavong A, Norman PS Jr, et al. Immunotherapy for cat asthma. J Allergy Clin Immunol 1988;82:1055-68.
351. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, Kagey-Sobotka A, Khattignavong A, Norman PS Jr, et al. Immunotherapy decreases skin sensitivity to cat extract. J Allergy Clin Immunol 1989;83:888-99.
352. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinnepain MT, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. Clin Exp Allergy 2001;31:988-96.

APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract components

Tree	T
Grass	G
Bermuda	B
Weeds	W
Ragweed	R
Mold	M
Alternaria	Alt
Cladosporium	Cla
Penicillium	Pcn
Cat	C
Dog	D
Cockroach	Cr
Dust mite	DM
D farinae	Df
D pteronyssinus	Dp
Mixture	Mx

APPENDIX 3. Example of a build-up schedule for weekly immunotherapy

Dilution (vol/vol)	Volume (mL)
1:1000	0.05
	0.10
	0.20
	0.40
1:100	0.05
	0.10
	0.20
	0.30
	0.40
	0.50
1:10	0.05
	0.07
	0.10
	0.15
	0.25
	0.35
	0.40
	0.45
	0.50
Maintenance concentrate	0.05
	0.07
	0.10
	0.15
	0.20
	0.25
	0.30
	0.35
	0.40
	0.45
	0.50

Dilutions are expressed as vol/vol from the maintenance concentrate.

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.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

Visit	Dose (mL)	Concentration as dilution of maintenance vial
1	0.10	1:1000 vol/vol
	0.40	1:1000 vol/vol
	0.10	1:100 vol/vol
2	0.20	1:100 vol/vol
	0.40	1:100 vol/vol
	0.07	1:10 vol/vol
3	0.10	1:10 vol/vol
	0.15	1:10 vol/vol
	0.25	1:10 vol/vol
4	0.35	1:10 vol/vol
	0.50	1:10 vol/vol
5	0.07	1:1 vol/vol
	0.10	1:1 vol/vol
6	0.15	1:1 vol/vol
	0.20	1:1 vol/vol
7	0.30	1:1 vol/vol
	0.40	1:1 vol/vol
8	0.50	1:1 vol/vol

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a legend should be included to describe the meaning of the abbreviations.

Allergen immunotherapy extract content information:

- The following information for each allergen should be included on the form in a separate column:
  Content of the allergen immunotherapy extract, including common name or genus and species of individual antigens and detail of all mixes, should be included.
- Concentration of available manufacturer's extract should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. This can be calculated by dividing the projected effective concentration by the concentration of available manufacturer's extract times the total volume.
- The type of diluent (if used) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription form

Allergen Immunotherapy Extract Prescription Form

Patient Name:
Patient Number:
Birth Date:
Telephone:

Prescribing Physician:
Address:

Telephone:
Fax:

Allergen Extract Name:

Bottle Name Abbreviations

Tree: T	Mold: M
Grass: G	Cat: C
Weed: W	Dog: D
Ragweed: R	Cockroach: Cr
Mixture: Mx	Dust Mite: Dm

Maintenance Concentrate Prescription Form

Prepared by: _____ **Date Prepared:**__/__/__

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__

Antigen Number	Extract Name Allergen or Diluent (Common name or *Genus/species*)*	Concentration and Type Manufacturer's Extract (AU, BAU, W/V, PNU)/ (50% G, Aq, Ly, AP)	Volume of Manufacturer's Extract to Add	Extract Manufacturer	Lot Number	Expiration Date
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
Diluent						
Total Volume						

*** Components of mixes listed on a separate sheet**

Volume to add = $\frac{\text{Maintenance Concentration}}{\text{Conc. Of Manufacturer's Extract}}$ x Total volume

Specific Instructions:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

Maintenance concentration and subsequent dilutions reported as volume/volume (v/v) dilutions with maintenance concentration=1:1 v/v

BAU = Bioeqivalent Allergy Unit, AU =Allergy Unit
PNU=Protein Nitrogen Unit
W/V=Weight per Volume Ratio
G= 50 % Glycerinated
Aq=Aqueous, Ly=Lyophilized
AP= Alum precipitated, AcP= Acetone precipitated

APPENDIX 8. Maintenance concentrate prescription form

Patient Name: Jerry Cleanex
Patient Number: 23456
Birth Date: 05/05/90
Telephone: 645-345-0987

Prescribing physician: Dr. Ah Choo
Address: 665 Rosebud Lane
Hollywood, Fl. 33424
Telephone: 645-123-4444
Fax: 645-123-4567

Vaccine Name: C, R, G, T, W

Maintenance Concentrate Prescription Form

Bottle Name Abbreviations

Tree: T	Mold: M
Grass: G	Cat: C
Weed: W	Dog: D
Ragweed: R	Cockroach: Cr
Mixture: Mx	Dust Mite: Dm

Prepared by: Mary Lancet Date Prepared: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
Vial _____ from Vial _____ on ____/____/____ Expiration date: ____/___/____
Vial _____ from Vial _____ on ____/____/____ Expiration date: ____/____/____
Vial _____ from Vial _____ on ____/____/____ Expiration date: ____/____/____

Antigen Number	Extract Name Allergen or Diluent (Common name or *Genus,species*)*	Concentration and Type Manufacturer's Extract (AU, BAU, W/V, PNU)/ (50% G, Aq, Ly, AP)	Volume of Manufacturer's Extract to Add**	Extract Manufacturer	Lot Number	Expiration Date
1	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

Volume to add = $\frac{\text{Maintenance Concentration}}{\text{Conc. Of Manufacturer's Extract}}$ x Total volume

Specific Instructions:

_____

_____

Prescribing Physician Signature

Maintenance concentration and subsequent dilutions reported as volume/volume (v/v) dilutions with maintenance concentration=1:1 v/v

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

The purpose of the allergen immunotherapy administration form is to document the administration of the allergen immunotherapy extract to a patient. Its design should be clear enough so that the person administering an injection is unlikely to make an error in administration. It also should provide documentation in enough detail to determine what was done on each visit. The following recommendations on allergen immunotherapy are taken from The Joint Task Force on Practice Parameters.

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

Allergen Immunotherapy Administration Form

Patient Name: **Date of Birth:**
Patient Number:
Telephone Number: **Diagnosis:**

Prescribing Physician:
Address:

Telephone: **Fax:**

Dilution Color	1:10,000 (v/v) Silver	1:1000 (v/v) Green	1:100 (v/v) Blue	1:10 (v/v) Yellow	Maintenance 1:1 (v/v) Red
Vial number	5	4	3	2	1
Expiration date(s)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___

Immunotherapy	A	B
Date started		
Date maintenance dose reached		
Maintenance dose		
Maintenance interval		

Best Baseline Peak Flow: _____
Baseline Blood pressure: _____

Allergen extract: ***contents***

	Date	Time	Health screen abnormal[1]	Anti-histamine taken?[2] or premed	Peak Flow	Arm	Vial Number or Dilution	Delivered Volume	Reaction[3]	Injector Initials
1.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
2.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
3.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
4.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
5.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
6.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
7.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
8.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
9.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
10.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
11.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
12.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
13.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
14.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
15.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
16.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
17.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
18.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
19.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
20.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
21.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
22.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
23.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____
24.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	_____

1. **Health screen** *refers to either a written or verbal interview of the patient prior to the administration of the allergy injection regarding: the presence of increased allergy or asthma symptoms or symptoms of respiratory tract infection, beta-blocker use, change in health status (including pregnancy) or adverse reaction to previous injection. A* ***yes*** *answer to this health screen may require further evaluation (see health screen record on back page).*

2. **Antihistamine use:** *to improve consistency in interpretation of reactions it should be noted if the patient has taken an antihistamine on injection days. Physician may also request that* ***antihistamines be taken consistently on injection days****:* ***recommended: Y N***

3. **Reaction**: *refers to either immediate or delayed systemic or local reactions. Local reactions (noted as LR) can be reported in millimeters as the longest diameter of wheal and erythema.. The details of the symptoms and treatment of a* ***systemic reaction*** *(noted as* ***SR****) would be recorded elsewhere in the medical record. Guidelines for dose reduction after a systemic reaction on a separate instruction sheet.*

Injector signature	Initials

Projected Build-up Schedule						
Vial 5	Vial 4	Vial 3	Vial 2		Vial 1	

Date to reorder: __/__/__

Allergen Immunotherapy Administration Form

Patient Name: **Date of Birth:** **Patient Number:** **Telephone Number:** **Diagnosis:**	**Prescribing Physician:** **Address:** **Telephone:** **Fax:**

Dilution Color	**1:10,000 (v/v) Silver**	**1:1000 (v/v) Green**	**1:100 (v/v) Blue**	**1:10 (v/v) Yellow**	**Maintenance 1:1 (v/v) Red**
Vial number	**5**	**4**	**3**	**2**	**1**
Expiration date(s)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___

Immunotherapy	**A**	**B**
Date started		
Date maintenance dose reached		
Maintenance dose		
Maintenance interval		

Best Baseline Peak Flow: _____
Baseline Blood pressure: _____

Allergen extract: ***contents***

Allergen extract B: _____

	Date	**Time**	**Health screen abnormal[1]**	**Anti-histamine taken?[2] or premed**	**Peak Flow**	**Arm**	**Vial Number or Dilution**	**Delivered Volume**	**Reaction[3]**	**Arm**	**Vial Number or Dilution**	**Delivered Volume**	**Reaction**	**Injector Initials**
1.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
2.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
3.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
4.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
5.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
6.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
7.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
8.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
9.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
10.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
11.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
12.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
13.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
14.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
15.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
16.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
17.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
18.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
19.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
20.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
21.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
22.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
23.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____
24.	___/___/___	_____	Y N	Y N	_____	R L	_____	_____	_____	R L	_____	_____	_____	_____

1. **Health screen** *refers to either a written or verbal interview of the patient prior to the administration of the allergy injection regarding: the presence of increased allergy or asthma symptoms or symptoms of respiratory tract infection, beta-blocker use, change in health status (including pregnancy) or adverse reaction to previous injection. A* ***yes*** *answer to this health screen may require further evaluation (see health screen record on back page).*

2. **Antihistamine use:** *to improve consistency in interpretation of reactions it should be noted if the patient has taken an antihistamine on injection days. Physician may also request that* ***antihistamines be taken consistently on injection days****:* ***recommended: Y N***

3. **Reaction**: *refers to either immediate or delayed systemic or local reactions. Local reactions (noted as LR) can be reported in millimeters as the longest diameter of wheal and erythema.. The details of the symptoms and treatment of a* ***systemic reaction*** *(noted as* ***SR****) would be recorded elsewhere in the medical record. Guidelines for dose reduction after a systemic reaction on a separate instruction sheet.*

Injector signature	**Initials**

Date to reorder: __/__/__

Projected Build-up Schedule						
Vial 5	**Vial 4**	**Vial 3**	**Vial 2**		**Vial 1**	

APPENDIX 12. Health screen record

Patient name:_____ **Date of birth:**_____ **Patient number**_____

Health Screen Record

1. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

2. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

3. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

4. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

5. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

6. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

7.Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

8.Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

9.Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any) : _____

10. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

11. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

12. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

APPENDIX 13. Allergen immunotherapy informed consent

- Documentation that informed consent has been obtained.
- Informed consent is a process by which a patient and physician discuss various aspects of a proposed treatment. Although many allergists use a written consent form before starting immunotherapy, a reasonable alternative is simply to document the consent process in the medical record. The consent process usually consists of the following:
  - what the treatment is and alternatives to the treatment;
  - potential benefits to be expected from the treatment;
  - potential risks, including a fair description of how frequently they are likely to occur, if known, including the possibility of death;
  - costs associated with immunotherapy and who pays for them;
  - the anticipated duration of treatment; and
  - any specific office policies that affect treatment.
- Since the informed consent process is complex and details might vary from state to state, each allergist/immunologist should decide how they should document informed consent. Legal advice might be useful.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis treatment record

Allergen Immunotherapy Systemic Reaction/Anaphylaxis Treatment Record

Name:_____ **Date:**_____

Date of Birth:_____ **Prescribing Physician:**_____

Allergens: Tree-Grass-Weed-Mites-Cockroach-Animal Dander-Mold-Hymenoptera

Prior systemic rxn:_____ **Hx of asthma?**_____

Date/time of injection:_____ **Date/time of rxn:**_____

Dilution (Vial #): _____ **New? Yes No**

History of the systemic reaction (SR):

Immediate measures:
__Assess airway, breathing, circulation, and orientation
__Epinephrine IM into thigh
__Activate EMS (call 911 or local rescue squad) Y/N Time called:_____AM/PM
__Management algorithm reviewed (as needed)

Signs and Symptoms

Respiratory:	**Skin:**	**Eye/Nasal:**	**Vascular:**	**Other:**
Shortness of Breath	Hives	Runny Nose	Hypotension	Difficulty Swallowing
Wheezing	Angioedema	Red Eyes	Chest Discomfort	Abdominal pain, nausea, diarrhea
Cough	Generalized Itch	Congestion	Dizziness	Diaphoresis
Stridor	Flushing	Sneezing	Headache	

Time	**Resp. rate/ PEFR**	**Pulse/ O2 Saturation**	**BP**	**Intervention, Medications, Exam Comments**

Time of discharge from the office:_____ **Condition upon release:**
_____

_____
Patient instructions:
_____
Follow-up call to patient:
Time_____
Comments:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

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

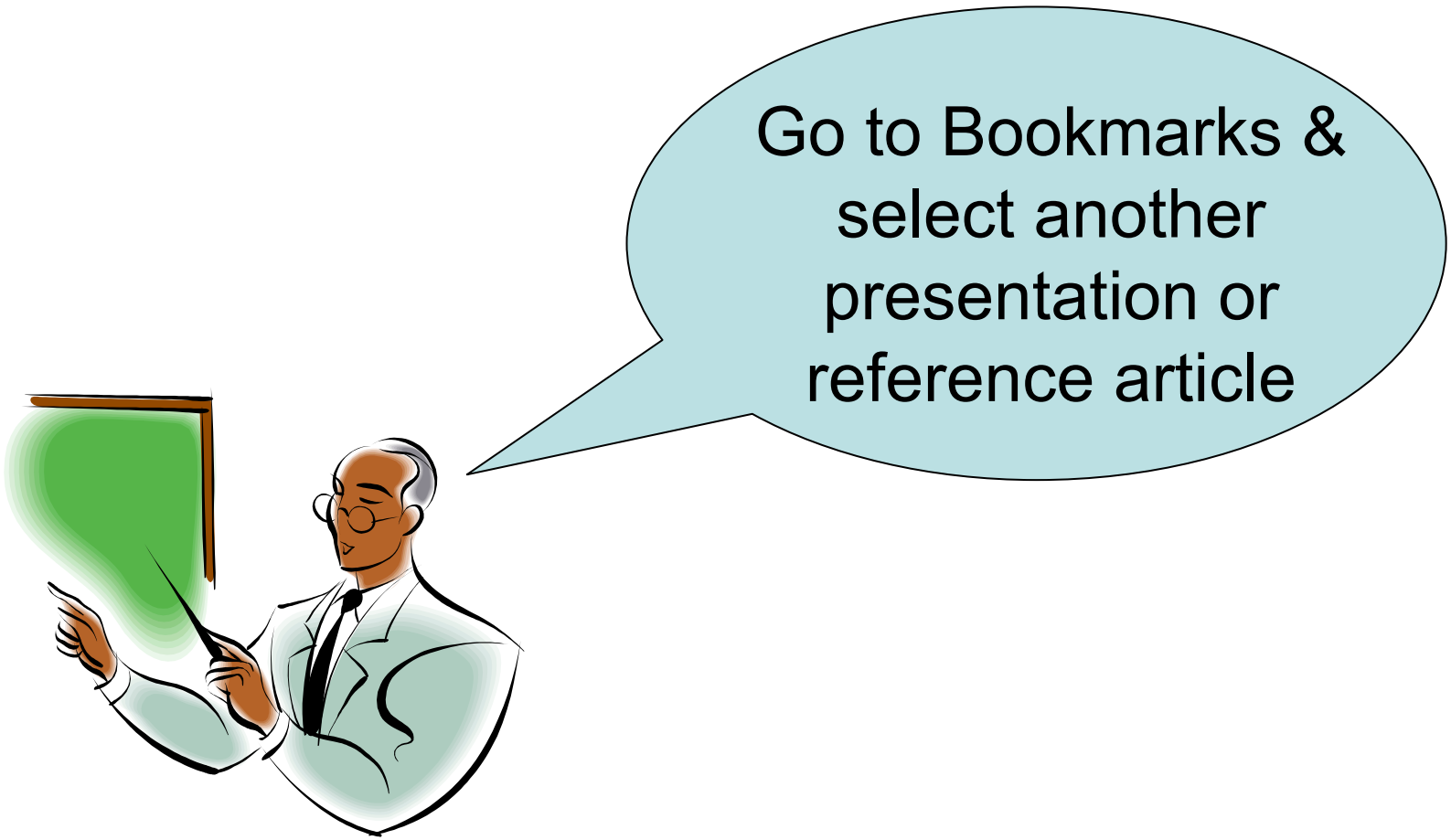
6+ = Cardiopulmonary arrest

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.

End of Selection



Immunotherapy Safety for the Primary Care Provider
Self-Assessment Test

1. Allergen immunotherapy is NOT indicated for:
   a. Allergic asthma
   b. Chronic urticaria
   c. Venom hypersensitivity
   d. Allergic rhinitis

2. Anaphylaxis can be triggered by bee stings, foods, allergy shots, and vaccines.
   a. True
   b. False

3. Patients should remain in the physician's office at least ____ minutes after an allergen injection.
   a. 10 minutes
   b. 30 minutes
   c. 60 minutes
   d. 120 minutes

4. Who can NOT initiate treatment with Epinephrine during anaphylaxis?
   a. Any trained technician (trained Corpsman/Medic) or licensed provider
   b. Any Corpsman/Medic under the "Ferris Doctrine"
   c. Any trained friend or family member under the "Good Samaritan Law"
   d. The trained patient to themselves

5. Risk factors associated with immunotherapy include all of the following EXCEPT:
   a. Concurrent beta blocker use
   b. Poorly controlled asthma
   c. Concurrent use of antihistamines which may mask systemic reactions
   d. Injections given from a new vial

6. When starting an AEROALLERGEN REFILL vial, by how much should you decrease the dose?
   a. 10%
   b. 90%
   c. 50%
   d. 25%

7. What was the recommended color of the cap for the maintenance (1:1 v/v) AIT vial?
   a. Red
   b. Yellow
   c. Blue
   d. Silver

8. Allergy shots are administered:
   a. Intramuscular (IM)
   b. Subcutaneous (SQ)
   c. Intradermal (ID)
   d. Oral (PO)

9. A patient reports to you 10 minutes after her allergy injection that she is sneezing, having itchy eyes, and chest congestion with coughing. What is the treatment of choice?
   a. Administer epinephrine intravenously
   b. Administer epinephrine intramuscularly
   c. Administer steroids by injection
   d. Administer albuterol by nebulizer

10. A patient is on his monthly maintenance (0.5 cc of 1:1 v/v) aeroallergen immunotherapy. He comes 4 weeks after his last shot, but now has a new (just refilled) vial. What dose should he get today?
   a. 0.50 cc of the renewed maintenance (1:1) vial
   b. 0.25 cc of a diluted (1:10) step-down vial
   c. 0.05 cc of the renewed maintenance (1:1) vial
   d. 0.25 cc of the renewed maintenance (1:1) vial

11. All of the following are ABSOLUTE contraindications for initiating venom immunotherapy EXCEPT:
   a. Pregnancy
   b. Severe COPD
   c. Unstable angina
   d. Patient taking a beta-blocker

12. After the initiation of AIT, when should the patient be routinely re-evaluated by the Allergist?
   a. Monthly
   b. Quarterly
   c. Annually
   d. At the conclusion of his/her AIT (i.e., 3-5 years)

13. A patient reports that he had swelling down to his elbow after the last allergy shot and it lasted for greater than 12 hours. What adjustments should be made?
   a. No adjustment required – advance per routine advancement protocol
   b. Make adjustments as directed by the Allergist's dose adjustment instructions
   c. Do not give a shot today and advise the patient to return after having taken ibuprofen
   d. Treat the reaction as a systemic considering the size of the swelling

14. Can a trained technician administer epinephrine in the absence of a physician?
   a. Yes
   b. No

15. A 12 yo male presents for his allergy injection. He has asthma and is on several medications. His mother stated that after his last injection, he had an increase in coughing, but no wheezing or other chest complaints. The coughing continued through the night but resolved the next day. What dose of his immunotherapy would you administer next?

a. Repeat the last dose given since this may be the patient's baseline
b. Advance as per protocol since this may be the patient's baseline
c. Decrease or hold the dose per allergist's dose adjusting instructions as if the patient had a systemic allergic reaction from the last injection
d. Decrease by 25% after pretreating with albuterol and Benadryl before today's shot

16. A patient comes in for her shot. She has asthma; therefore pulmonary function testing is done prior to her shot. Her Peak Flow is 24% lower than her normal baseline. It is permissible to give her allergy shot today.

a. Yes
b. No

17. You DO NOT reduce the first dose when administering venom from a refill vial.

a. True
b. False

18. You have received a set of new vials for a patient. The vials have red tops and previously the vials had blue tops. The accompanying schedule directs that the vial progression is from green to blue to yellow to red tops. What should you do?

a. Notify the prescribing allergist's office of a possible error and do not give any further injections until clarified
b. Give the recommended starting dose of 0.05 cc SQ per protocol
c. Give ½ of the recommended starting dose
d. Start over in the previous vials (blue tops)

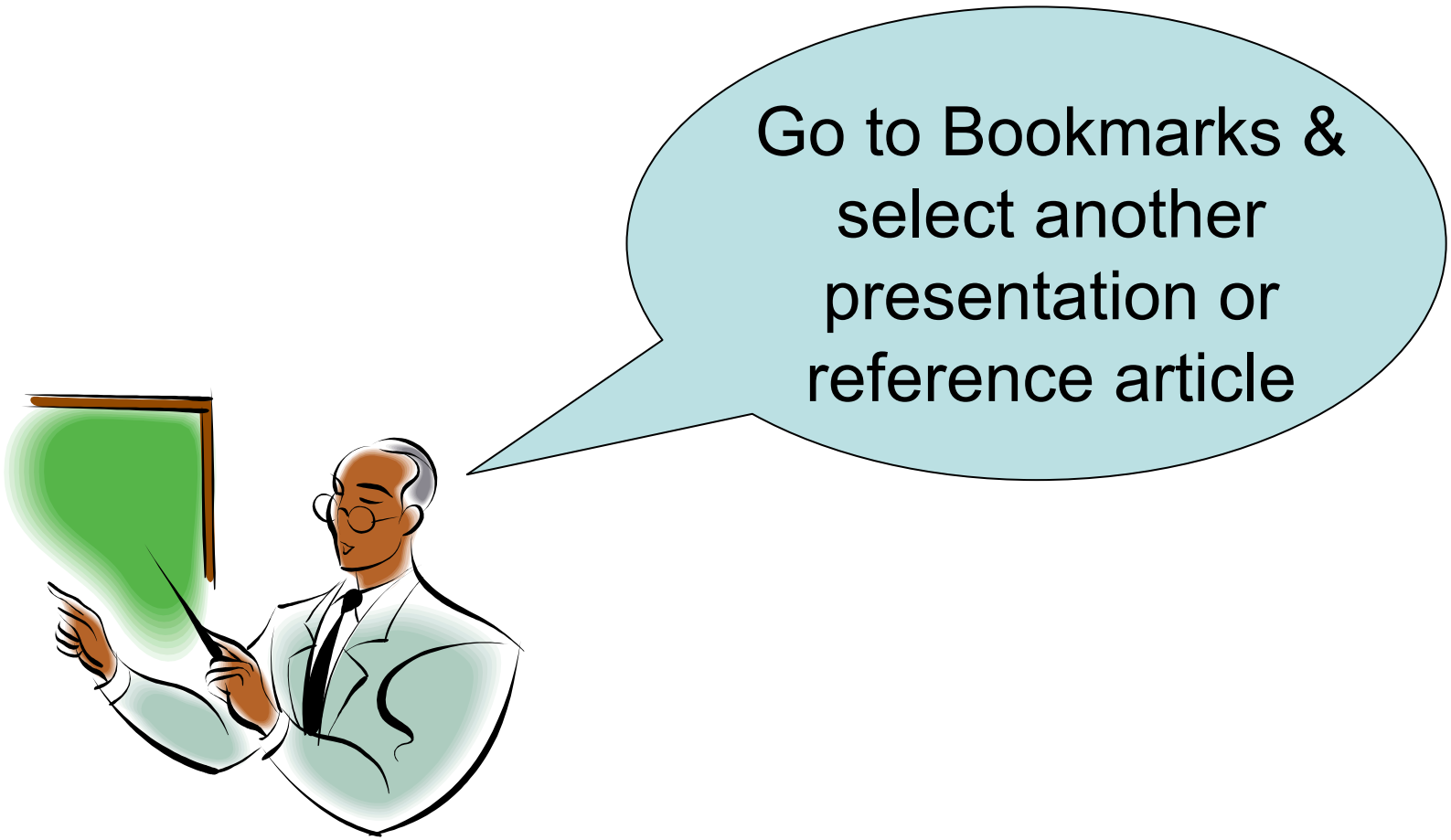
19. Your patient is 6 weeks late for his allergy shot and his Allergist has asked that you "reduce this shot by 75%". His last shot was 0.50 cc from his yellow (1:10 v/v) vial. Today's dose would be?

a. 0.1 cc from his yellow (1:10) vial
b. 0.4 cc from his blue (1:100) vial
c. 0.25 cc from his blue (1:100) vial
d. 0.05 cc from his yellow (1:10) vial

20. You decide in question #19 to give your patient a dose from his blue vial, but find his blue vial has expired. To make a blue vial from his yellow vial, you would…

a. Add 1.0 cc of yellow vial to 10.0 cc of sterile albumin/saline diluent
b. Add 0.05 cc of yellow vial to 4.5 cc of sterile albumin/saline diluent
c. Add 0.2 cc of yellow vial to 1.8 cc of sterile albumin/saline diluent
d. Add 3.0 cc of yellow vial to 9.0 cc of sterile albumin/saline diluent

End of Selection

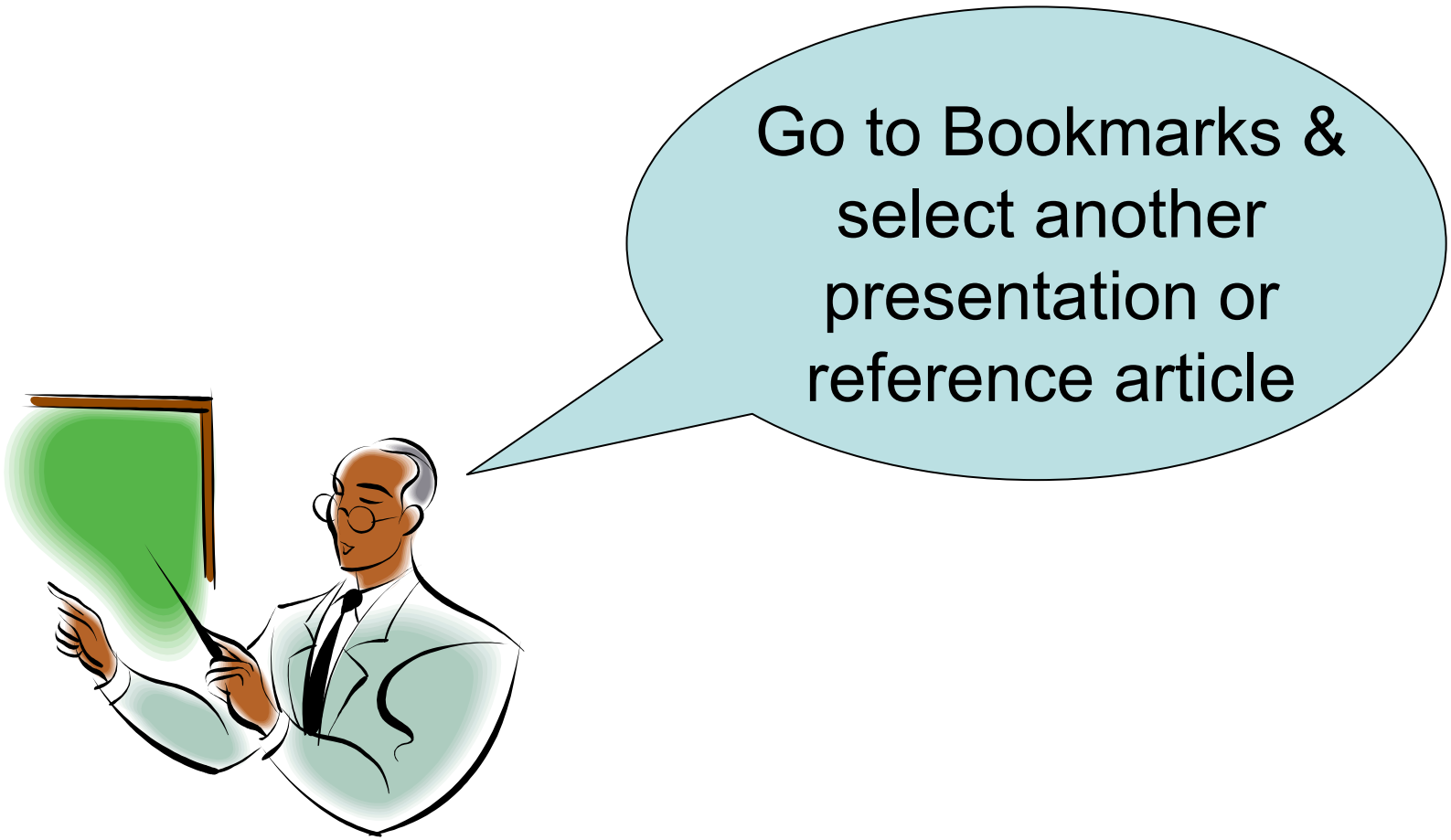


Immunotherapy Safety for the Primary Care Provider

Self-Assessment Test Answer Key

1. B
2. A
3. B
4. B
5. C
6. C
7. A
8. B
9. B
10. D
11. D
12. C
13. B
14. A
15. C
16. B
17. A
18. A
19. A
20. C

End of Selection




SITE UNDER
CONSTRUCTION

Anaphylactic/Anaphylactoid Reactions

Capt. Jay R. Montgomery MC, USN
Allergy and Immunology Service
National Naval Medical Center

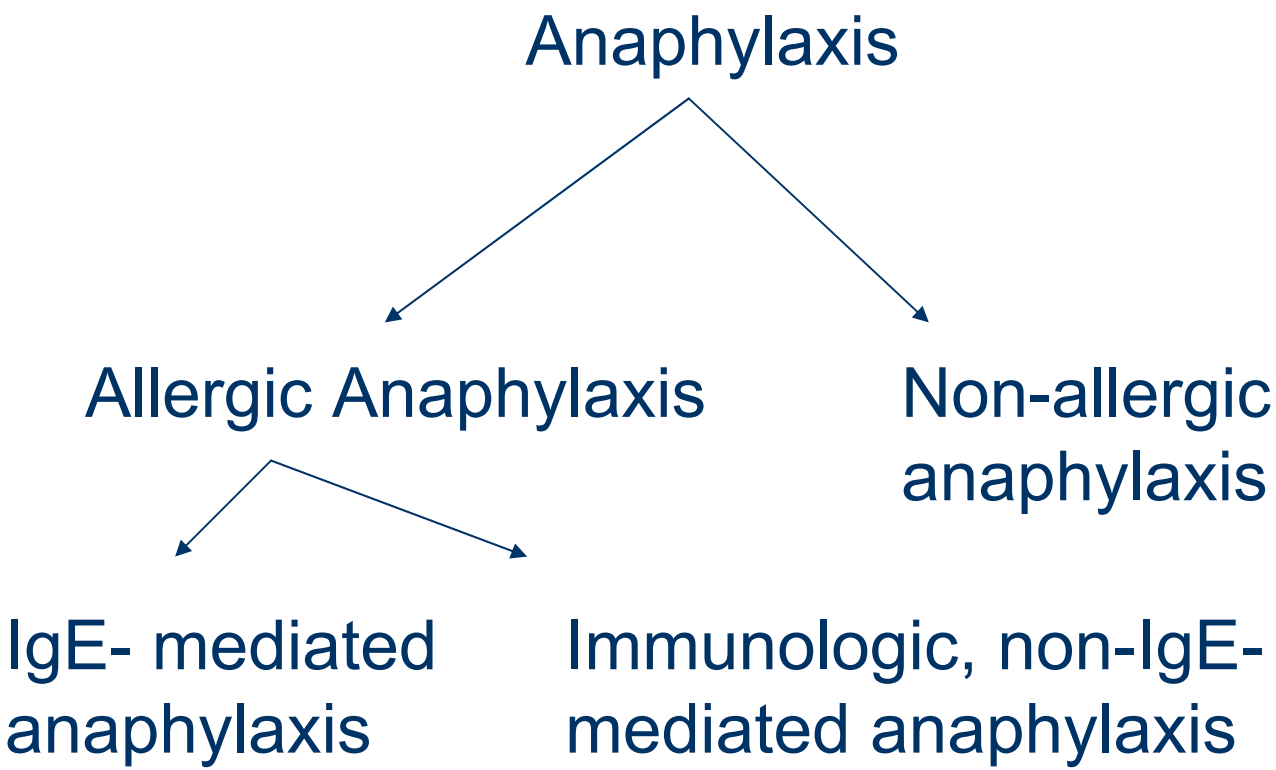
Introduction

- *"Anaphylaxis"*
  - Word first coined by Portier and Richet in 1902.
  - While attempting to immunize dogs to sea anemone venom, the dogs unexpectedly died after a previously non-lethal dose.
  - They had unwittingly sensitized the animals.
  - This phenomenon was opposed to their goal of prophylaxis so they referred to it as anaphylaxis, meaning "against protection".

Definition 101

- Anaphylaxis:
  - An acute systemic reaction caused by release of potent chemical mediators from mast cells, baso-phils, and secondarily recruited inflammatory cells. It may occur within a few minutes to a few hours and can be life threatening.
  - Signs & symptoms may be isolated to one or involve several organ systems.
  - Mediated through IgE and its receptor on the cell
- Anaphylactoid
  - Same as above, just disregard statement #3

Revised Nomenclature For Anaphylaxis



Johansson SGO et al JACI 2004,113:832-6

Anaphylaxis* Is Not Rare

Insect stings	3%	of adults
Food	1-3%	of children
Drugs	1%	of adults
RCM	0.1%	of cases
Immuno Tx	3%	of patients
Latex	1%	of adults

**urticaria/angioedema or dyspnea or hypotension*

Anaphylaxis* Is Not Rare

Estimated risk in US: 1-3%

Fatalities per year in the US:

- antibiotic-induced: 600
- food-induced: 150
- venom-induced: 50

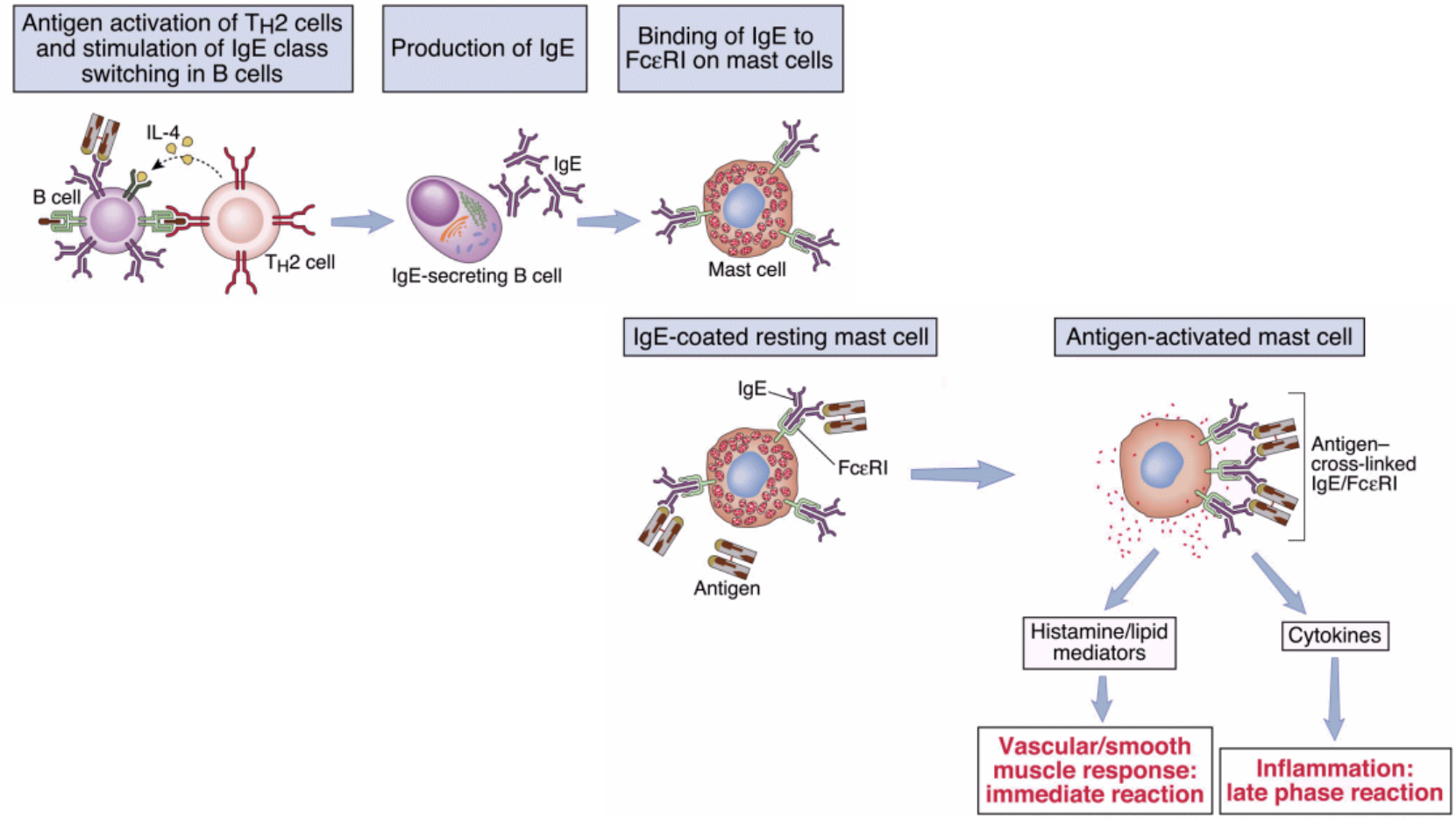
Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8

**urticaria/angioedema or dyspnea or hypotension*

Pathophysiology

- Activation of mast cells and basophils result in secretion of preformed mediators, followed by synthesis and secretion of lipid mediators and cytokines.
  - preformed granule-associated substances = histamine, tryptase, chymase, carboxypeptidase, & cytokines
  - newly-generated lipid-derived mediators = prostaglandin D2, leukotriene (LT) B4, LTC4, LTD4, LTE4, & platelet activating factor.

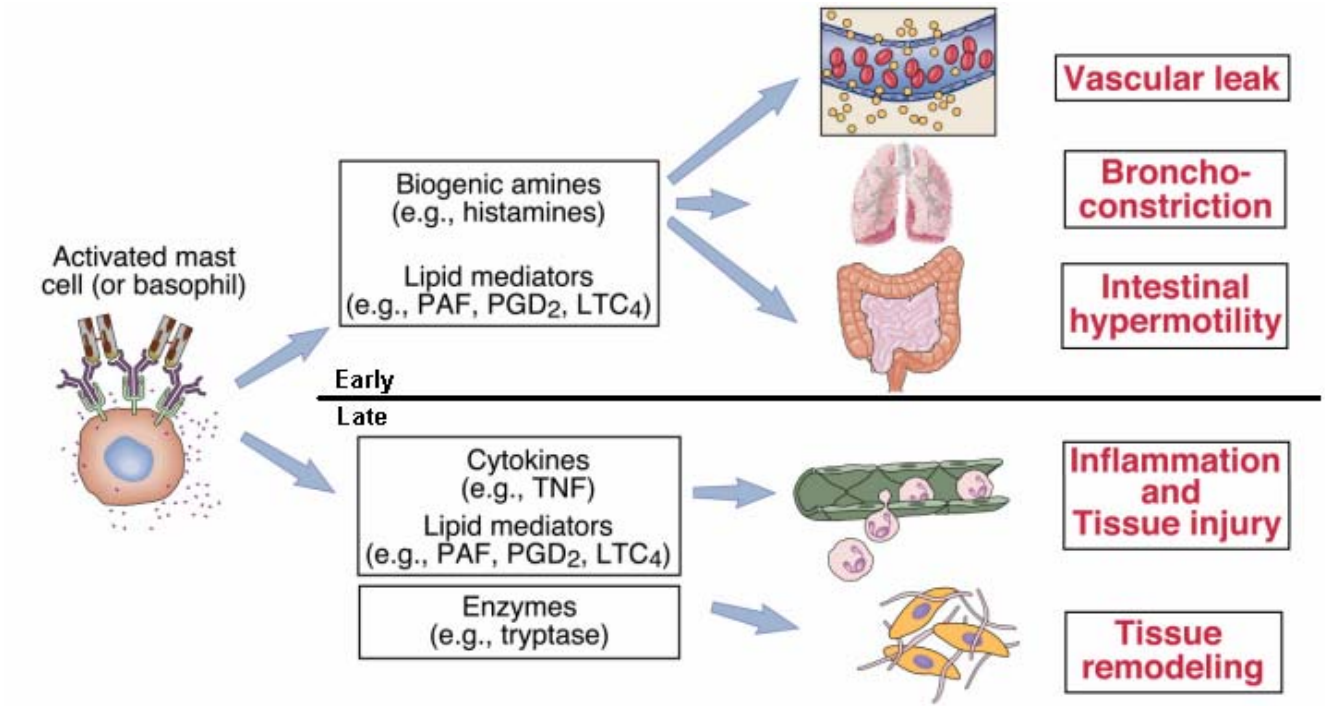
Pathophysiology



Pathophysiology

- The physiologic effects of the pre-formed mediators define the early phase anaphylactic reaction,
- While those of the synthesized cytokine IL-4, IL-5, IL-13, and chemokines shape the late phase inflammatory reaction.

Pathophysiology



Pathophysiology

- Major effects of mediators
  - Smooth muscle (bronchial/gut)spasm
  - profound myocardial depression
  - vasodilation, increase in vascular permeability can transfer 50% of IV fluid into EV space in 10 minutes
  - Death occurs via CV collapse or respiratory obstruction. Death occurred in < 1 hour in 70% (39/56) of patients in one study

Pathophysiology

- Histamine acts through H1 and H2 receptors
  - H1: pruritus, rhinitis, tachycardia, & bronchospasm
  - H1 & H2: headache, flushing, & hypotension
- Leukotrienes (LTB_4)
  - direct mast cell degranulation
  - chemotactic agents for late-phase inflammatory cells
- Complement (C5a)
  - direct mast cell degranulation
  - Induce smooth muscle ctx, increase vascular perm

Classification of Anaphylactic Syndromes

- IgE mediated
- Direct Mast-Cell Activation
- Complement Mediated
- Arachidonic Cascade Mediated
- Unknown Mechanisms

IgE Mediated Reactions

- Most Antibiotics
  - penicillins, cephalosporins, sulfonamides...
- Allergen Extracts
  - pollen, mold, dander, Hymenoptera & snake venom
- Vaccines
  - contaminated with egg, gelatin...
- Food
  - peanut, milk, egg, seafood, wheat, tree nuts
- Miscellaneous
  - insulin, formaldehyde, latex, streptokinase, seminal fluid...

Direct Mast Cell Releasers

- Opiates
- Hypertonic solutions
  - Radiocontrast media, Mannitol
- Polysaccharides
  - dextran, iron-dextran
- Other Drugs
  - curare, succinylcholine, vancomycin, ciprofloxacin
- Exercise (?)
- Physical stimuli (?)

Complement-mediated

- C5a, C3a, C4a (anaphylotoxins)
  - plasma
  - immunoglobulins
  - dialysis membranes

➔ Direct mast cell degranulation

Arachidonic Cascade-mediated

- Nonsteroidal anti-inflammatory agents
  - COX1
  - COX2 (?)
- Increase in Leukotrienes through blockade of prostaglandin synthesis pathway(s)

➔ Direct mast cell degranulation

Unknown Mechanisms

- Exercise-induced anaphylaxis
- Cholinergic urticaria w/ anaphylaxis
- Cold-induced urticaria w/ anaphylaxis
- Mastocytosis
- Sulfites
- Steroid preparations
  - progesterone, hydrocortisone

Signs and Symptoms

- Cutaneous
  - Flushing, erythema, pruritus, urticaria, angioedema
- Gastrointestinal
  - Abdominal cramping, nausea/vomiting,diarrhea
- Reproductive
  - Uterine cramping
- Respiratory
  - Rhinitis, upper airway obs. from angioedema of tongue, oropharynx, & larynx. Lower airway obs. from bronchospasm
- Cardiovascular
  - Hypotension, arrhythmias, hypovolemic shock (severe & refrac.)

Anaphylaxis
Summary of Signs & Symptoms

- Flushing/urticaria/angioedema >90%
- Upper airway symptoms 56%
- Lower airway symptoms 47%
- Gastrointestinal symptoms 30%
- Cardiovascular Shock 10-30%
- Feeling of impending doom, metallic taste

Lieberman P. In: Middleton's Allergy: Principles and Practice, 6th edition, Mosby Inc., St. Louis, MO, 2003

Anaphylaxis
Summary of Signs & Symptoms

- Uniphasic (52%)
  - Abrupt and severe with death in minutes despite treatment
  - Gradual increase in symptoms
- Biphasic (7-20%)
  - Immediate symptoms, then an asymptomatic period from 1-8 hours, then recurrence of severe symptoms
- Protracted (28%)
  - Symptoms persisting for hours

Lieberman P. Ann Allergy Asthma Immunol 2005;95:217-26

Differential Diagnosis

- **Pulmonary**
  - Epiglottis, PE, foreign body aspiration, hyperventilation, asphyxiation
- **Cardiovascular**
  - MI, arrhythmia, cardiac arrest, hypovolemic shock
- **CNS**
  - Vasovagal rxn, CVA, seizures, drug overdose
- **Endocrine**
  - Carcinoid, pheochromocytoma, hypoglycemia
- **Other**
  - Mastocytosis, H/AAE, idiopathic urticaria, serum sickness, scombroid poisoning, VCD, panic attack

Montanaro A and Bardana EJ Jr. J Investig Allergol Clin Immunol 2002;12:2-11

Anaphylaxis Grading Scale I

- **Severe Anaphylaxis (likely to progress to hypotension/hypoxia)**
  - Confusion, fainting, unconsciousness, incontinence
- **Moderate Anaphylaxis (weakly associated with hypotension/hypoxia)**
  - Diaphoresis, vomiting, lightheadedness, dyspnea, stridor, wheezing, throat/chest tightness, nausea, abdominal pain
- **Mild Anaphylaxis (not associated with hypotension/hypoxia)**
  - Flushing, urticaria, erythema, angioedema (reactions limited to the skin alone)

Anaphylaxis Grading Scale II

- **Anaphylaxis is likely when 1 of 3 fulfilled:**
  1. **Acute onset with:**
     a) **Skin/mucosa AND**
     b) **Airway compromise OR**
     c) **Reduced BP**
  2. **Two or more of the following:**
     a) **Hx of severe reaction**
     b) **Skin/mucosa involvement**
     c) **Airway compromise**
     d) **Reduced BP**
     e) **Crampy abdominal pain, vomiting**
  3. **Hypotension after known exposure, angioedema (reactions limited to the skin alone)**

Anaphylaxis
In The Emergency Department

- Chart review in 21 American Emergency Departments
- Random sample of 678 pts presenting with food allergy
- Management:
  - 72% received antihistamines
  - 48% received systemic corticosteroids
  - 16% received epinephrine (24% of those with severe reactions)
  - 33% received respiratory medication (eg. inhaled albuterol)
  - only 16% received Rx for self-injectable epinephrine at discharge
  - only 12% referred to an allergist

Clark S et al. J Allergy Clin Immunol 2004;347-52

Laboratory Studies

- IgE antibodies to suspected allergen by either skin testing or RAST
- Histamine, plasma & urinary (max at 15 mins)
- Tryptase (peaks at 1-2 hours)
- Other
  - 5-HIAA, VMA, metanephrines, catecholamines

Guidelines for Treatment

- Assessment TO BE PERFORMED AT THE TIME OF ADMINISTRATION OF **EPINEPHRINE**.

  - Remove or discontinue of inciting agent (Infusion, stinger, etc.)
  - Examine upper/lower airway patency, secure airway
  - Place patient in recumbent position and elevate his/her legs
  - Monitor vital signs (P, BP, RR)
  - Monitor level of consciousness/mentation

Guidelines for Treatment

- Treatment (Airway/Breathing)
  - Maintain an open airway
  - High flow Oxygen (4-10 l/m) with pulse oximetry monitoring
  - Intubation when $PaCO_2$ > 65 mm Hg. / SaO_2 < 90% on O_2
- Treatment (Circulation)
  - Keep Systolic BP > 90 mm Hg
  - Place patient in Trendelenburg position as appropriate.
  - Insertion of large-bore IV
    - 0.9% saline or lactated ringer's
  - Severe Hypotension
    - Dextran, Hetastarch

Guidelines for Treatment

- Treatment (Drugs - ABC)
  - EPINEPHRINE (Adrenalin)
    - α and β adrenergic effects
    - 0.3-0.5 cc 1:1,000 IM q 5-15 min
  - Antihistamines (Benadryl)
    - H1 - diphenhydramine (Benadryl): 50 - 75 mg IM/IV
    - H2 - ranitidine (Zantac): 150mg q8-12 hr PO, 50mg q6-8 IV
  - Corticosteroids
    - Methylprednisolone IV 60 - 80 mg followed by predinsone

Kemp S and Lockey R. J Allergy Clin Immunol 2002;110:341-8
Simons FER et al. J Allergy Clin Immunol 1998;101:33-7
Simons FER et al. J Allergy Clin Immunol 2001;108:871-3

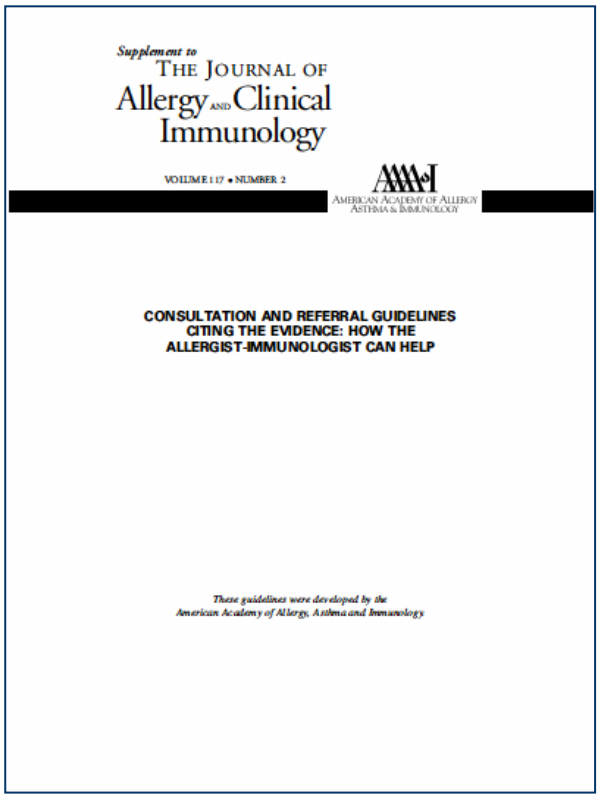
Guidelines for Treatment

- Treatment (Drugs)
  - For Myocardial depression
    - Epinephrine 0.1-0.2 cc 1:1,000 diluted in 10ml NS
    - Dopamine 2-20 µg/kg/min
  - For patients on β-blockers w/ refractory shock
    - Glucagon 1-5 mg over 2-5 min IV push
    - Isoproterenol 2-10 ug/min
    - Methylprednisolone, 1- 2 mg/kg per 24 hr
  - For Bronchospasm
    - Albuterol MDI/Nebulized (2.5 - 5 mg in 3 ml normal saline)

Prevention: How to Reduce Incidence

- General measures
  - Thorough history for drug, food, and other avoidable allergens
  - Avoid cross reacting drugs
  - Administer drugs orally
  - Check all drugs for proper labeling
  - Keep patients in office 20-30 minutes after injections (for immunotherapy or vaccination)
  - Evaluation by Allergist if in doubt

How the Allergist/Immunologist Can Help…



- Refer patients with:
  - A severe allergic reaction (anaphylaxis) without an obvious or previously defined trigger.
  - Anaphylaxis attributed to food.
  - Exercise-induced anaphylaxis
  - Drug-induced anaphylaxis

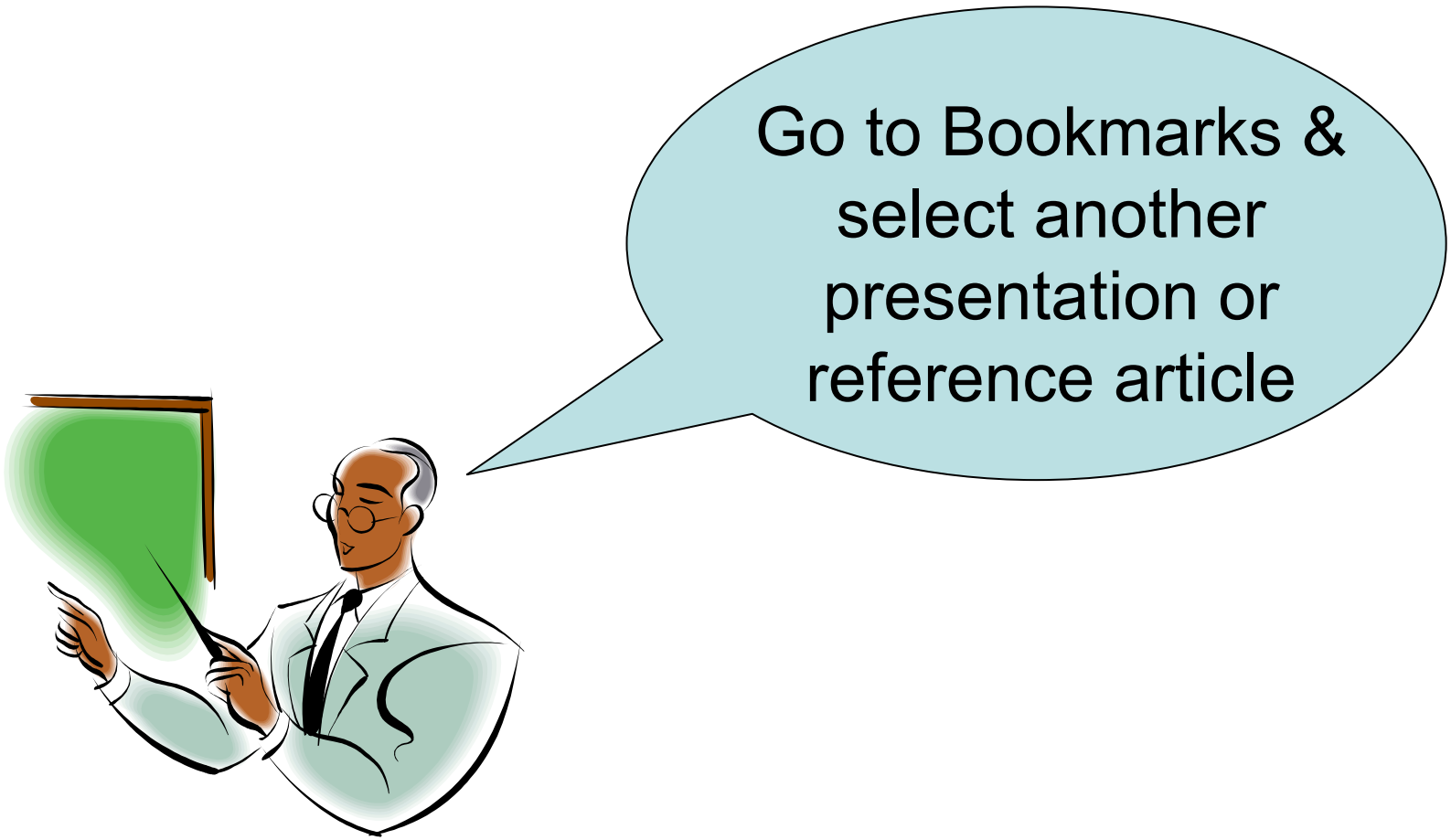
Prevention: Who is at risk?

- Prior history of anaphylaxis
- β-blockade therapy
- ACE-Inh therapy (?)
- Multiple antibiotic sensitivity syndrome
- Atopic background (latex anaphylaxis & possibly RCM anaphylactoid rxn; *not* venom or PCN)
- Unstable, steroid-dependent asthma

Summary

- Anaphylaxis: release of inflammatory mediators from mast cells & basophils (IgE-/non-IgE-mediated)
- Symptoms: within minutes of exposure to triggering agent (less commonly can be delayed or biphasic)
- Common triggers: drugs, foods, hymenoptera stings; idiopathic
- First-line of treatment: injected epinephrine
- Management: education and prevention

End of Selection



ANAPHYLAXIS

• First reported case was in 2640 BC – pharoh died from sting of wasp
• Occurs in 1 of every 3,000 hospitalized patients
• Annual deaths: at least 500
• No known epidemiologic characteristics that reliably identify those at risk
• Most studies suggest that an atopic person is at no greater risk

Mast Cell Mediators:

Once stimulated, the mast cells secrete two groups of mediators:

1) preformed mediators and
2) newly formed mediators.

• The preformed mediators have been synthesized in advance and stored in granules, to be released immediately upon stimulation of the mast cell. This group of mediators include histamine, proteolytic enzymes (tryptase), heparin, and chemotactic factors.
• The newly formed mediators consists of lipids that are synthesized after the mast cell is stimulated. The stimulus activates phospholipase A2, which acts to break down phospholipids in the cell membrane to arachidonic acid. Arachidonic acid can then either enter the cyclo-oxygenase pathway to produce prostaglandins and thromboxanes or the lipoxygenase pathway, to produce the leukotrienes.

Mediator actions: These mediators rapidly act

- on the smooth muscle
  - in the lung to cause bronchospasm and
  - in the gastrointestinal tract to cause abdominal cramping and diarrhea.
- on the bronchial airways to produce
  - increased mucus production and
  - an inflammatory infiltrate
- on the circulatory system to produce
  - vasodilation and
  - increased vasculature permeability, leading to bronchial edema, urticaria, and hypotension.

Tryptase. The biologic action of tryptase in anaphylactic reactions remains uncertain; however, it can serve as an important marker of anaphylaxis.

• Whereas histamine is very transient and difficult to measure, tryptase doesn't peak until 1-2 hours after the stimulus and remains in the circulation up to 6-8 hours. The detection of tryptase in the serum can serve to confirm your suspicions when a patient presents with symptoms of anaphylaxis.

Mast Cell Activation: Three main triggers of mast cell activation:

1) IgE hypersensitivity. Antigen crosslinks IgE antibodies attached to mast cells through Fc epsilon receptors. When it crosslinks two IgE molecules, it draws the attached IgE receptors close to one another. Such aggregation of receptors activates the cell.

2) Anaphylatoxins: C3a and C5a
3) Drugs: Certain drugs act directly on the mast cell to release its mediators.

Classification of Anaphylaxis: Most classification systems utilize these three mechanisms of mediator release to classify the various types of anaphylaxis:

1) IgE mediated anaphylaxis
2) Complement activated anaphylaxis
3) Mast cell/basophil activated anaphylaxis
4) Unknown/Idiopathic anaphylaxis

Anaphylaxis vs anaphylactoid: The term anaphylaxis is frequently used to refer only to IgE-mediated, mast cell activation, whereas anaphylactoid reactions are used to denote the other non-IgE mediated responses. However, both events are clinically and biochemically similar; therefore, the term "anaphylaxis" is often used interchangeably for both clinical syndromes.

Components of an IgE anaphylactic response:

1) Exposure to a sensitizing antigen
2) An IgE-class antibody response, resulting in systemic sensitization of mast cells or basophils
3) Reintroduction of the sensitizing antigen
4) Mast cell degranulation (with mediator release/generation)
5) Pathologic responses: anaphylaxis.

Examples of IgE-Mediated Reactions

1) Medications

- Penicillin: Penicillin and other beta-lactam antibiotics account for more than *75%* of cases of anaphylaxis from medication.
  - Most frequent cause of anaphylaxis: 400-800 deaths annually.
  - 1 case/2,500 course of penicillin given.
  - Skin testing: predictive.
- Local anesthetics:
  Reactions to local anesthetics are common; however, IgE mediated reactions are exceedingly rare. Most reactions are due to vasovagal, toxic, or idiosyncratic responses rather than true allergic reactions. Hypersensitivity more common with the preservatives in the anesthetic: parabens and sulfites.

2) Foreign proteins (horse serum, chymopapain, latex)

Latex: becoming especially important with the widespread use of latex gloves. It is particularly common in patients with spina bifida or congenital urologic abnormalities because of frequent exposure to urinary catheters and frequent operations. Should be considered whenever an intraoperative reaction occurs.

3) Foods (peanuts, nuts, fish, shellfish, egg, and milk) Concomitant asthma is an important risk factor.

4) Hymenoptera stings

Although almost *25%* of the population may be at risk, fewer than 100 deaths occur each year

5) Immunotherapy

Despite its widespread use, fatalities from allergen immunotherapy are extremely rare. (45 fatalities since 1945)

Complement mediated anaphylaxis. This type of anaphylaxis doesn't depend on IgE, but rather the other antibodies: IgG, IgM, and IgA antibodies. Both the classic complement pathway and the alternate pathway are implicated in the generation of anaphylatoxins, C3a and C5a. These products are then capable of causing mast cell (and basophil) degranulation.

The most classic examples of complement mediated anaphylaxis are reactions to blood and its products:

- Example 1: IgG aggregates (Gamma globulin)
  Administration of gamma globulin has been associated with anaphylactoid reactions because it contains IgG dimers and polymers capable of activating complement spontaneously.
    - Cl combines with the aggregated immunoglobulins and eventually leads to the production of C3 convertase and CS convertase which, in turn, result in the release of the anaphylatoxins C3a and C5a
    - Both C3a and C5a then act on the mast cell to promote mediator release.
- Example 2: IgG or 1gM anti-IgA
  Probably the best defined example is the anaphylaxis which can result when an IgA deficient patient receives blood products containing IgA. These patients frequently will produce IgG or 1gM anti-IgA antibodies, which will combine with the infused IgA in the administered blood products, and release anaphylatoxins.
    (IgA anaphylaxis can also occur through the more typical most cell sensitization with IgE anti -IgA)

Mast Cell Activated Anaphylaxis. Numerous agents have been reported to be capable of causing direct degranulation of mast cells with histamine release. The most clinically relevant are:

1. Opiates (generally limited to the skin)
2. Muscle relaxants (curare, d-tubocurarine)
3. Highly charged polyanionic antibiotics (polymyxin B)
4. Radiocontrast media *(Some sources suggest it might be complement mediated)*
    - Initial exposure: 1-10% risk of anaphylaxis (with conventional RCM)
    - Reexposure, in those with previous reaction: 17-35% risk of anaphylaxis
    - No *in-vitro* or *in-vivo* testing available (Not IgE mediated)
    - Rx -- prevent recurrence:
        - Pretreatment (Prednisone, Benadryl, and ephedrine)
        - Low osmolality RCM

Anaphylaxis of unknown origin:

1. Aspirin/NSAID
2. Sulfites (Na/K sulfites, bisulfites, metabisulfites)
3. Exercise
4. Hormones:

   A rare subset of women have cyclic anaphylaxis - often during the luteal phase of their menstrual cycle.

   • They may have positive skin tests to medroxyprogesterone, and
   • They may respond favorably to ovarian suppression or oophorectomy
5. Idiopathic:

   This group of patients experience recurrent anaphylaxis with no recognized cause.

   • The diagnosis is based on the typical signs and symptoms, as well as evidence of elevated urine histamine, elevated serum tryptase, and an exhaustive search for causative factors.

   • These patients all require an Ana-kit, and if anaphylaxis occurs frequently enough may require chronic steroid therapy to control their symptoms.

   • A subset of these patients even fail to respond to high-dose corticosteroid therapy - these patients are referred to as having malignant idiopathic anaphylaxis.

Acetylsalicylic acid (aspirin) and NSAID anaphylaxis

- Most likely mechanism is modulation of arachidonic acid metabolism by interference with cyclooxygenase enzyme pathways. There are two consequences of this action:
  1) reduction in the formation of prostaglandins, thromboxanes, and prostacyclin,
  2) enhanced formation of lipoxygenase products.
- In addition to enhanced mediator release, these patients may have an increased target-organ sensitivity to the leukotrienes.
- Rx: aspirin avoidance, desensitization, leukotriene receptor antagonists/lipoxygenase inhibitors.

Sulfite anaphylaxis. Should be suspected in individuals who have anaphylaxis associated with eating, particularly if restaurants or process foods are implicated.

• These patients may have such profound bronchoconstriction that they cannot speak and have been mistaken for a choking victim, occasionally having had the Heimlich maneuver performed on them.

• Sulfites are frequently utilized as preservatives and antioxidants. They are added to foods to prevent discoloration.

• Foods to which these substances are added in the highest concentrations include
  • leafy salad greens (salad-bar restaurants before restrictions).
  • light-colored fruits and vegetables (esp. dried fruits and instant potatoes)
  • wine and beer
  • fish and shellfish (particularly shrimp)

• Sulfites are also used as preservatives/antioxidants in a variety of medication. However, when compared with the amount of sulfite in foods, most pharmaceuticals contain small amounts of sulfite (0.25% to I %*)* However, the potential still exists, as these agents are either injected directly or inhaled by the patient.

• Sulfites are added to all the bronchodilator solutions of the catecholamine class to offset catecholamine susceptibility to inactivation by oxidation. Used primarily in the multidose vials -- but not in MDIs, because fluorocarbon propellant replaces sulfite as the preservative, and oxidation does not occur in these closed containers.

- Bronchodilator solutions: Bronkosol (the worst), Alupent, Isuprel
- Epinephrine
- Dopamine, norepinephrine
- Corticosteroids: Hydrocortisone, dexamethasone

Exercise-induced anaphylaxis. Recently a new group of patients have been described who experience urticaria and anaphylaxis on vigorous exercise, an entity termed exercise-induced anaphylaxis.

- This syndrome should be suspected in any person who collapses after exercise, particularly if flushing, urticaria, or angioedema are evident.
- Most of these events occur only very sporadically, and it was this intermittent nature that served as a clue that other associated factors may be responsible for promoting the occurrence.
- Many of these individuals only develop symptoms in the post-prandial period. In a survey of 199 patients, more than half of them felt that food ingestion 3 to 4 hours before exercise significantly increased their risk for anaphylaxis.
- Others report that a specific food ingested prior to exercise was a major factor: shellfish, celery, cabbage, chicken, or wheat products.
- Other associated factors: alcohol *(5%)*
  aspirin (6%)
  environmental factors (humidity: 63%)
  menstrual cycle (25% of women)

Clinical manifestations of anaphylaxis

- Onset: usually begins within minutes after exposure to the causative factor, although the onset may be delayed for several hours.
- Once under way, the reaction usually progresses in an explosive manner, reaching a peak intensity within 1 hour.
- The primary anaphylactic shock organs in humans are the cutaneous, gastrointestinal, respiratory, and cardiovascular systems, the latter two being the most critical.
  - Respiratory events: accounted for 70% of the mortality in one series,
  - Cardiovascular manifestations: accounting for an additional 24%
- Patients typically present with generalized pruritus (though often located to their palms, soles, or groin area) They get hives, angioedema and frequently are noted to have flushing.
- They often describe an immediate sense of impending doom - they know something is wrong. Other neurologic symptoms: weakness, dizziness, confusion, LOC, or seizures.
- Occasionally they complain of a metallic taste in their mouth, and are noted to have swelling of the lips and tongue.
- They frequently develop typical allergic symptoms
  - Itchy, watery, red eyes
  - Nasal congestion/rhinorrhea or sneezing

- In addition they may have:
    - Gastrointestinal symptoms:
        Nausea, vomiting, cramping, and diarrhea - sometimes bloody
    - Upper airway symptoms: (especially in children)
        Stridor secondary to laryngeal edema
        Early presentation may consist of
            hoarseness
            dysphonia, or
            "a lump in the throat"
    - Lower airway symptoms, typical of asthma:
        SOB, wheezing, and chest tightness
    - Cardiovascular symptoms:
        Hypotension, shock, and arrhythmias

Differential diagnosis

1. Loss of consciousness: In the diagnosis of sudden collapse in the absence of accompanying pruritus, urticaria and angioedema, one must consider several other disorders:
    - Cardiac arrhythmias
    - Myocardial infarction
    - Pulmonary embolism
    - Seizures
    - Asphyxiation/foreign body
    - Hypoglycemia
    - Vaso-vagal reaction: (Most common similar syndrome)
        - Patient collapses after an injection or painful situation
        - Bradycardia (rather than rapid, thready pulse of anaphylaxis)
        - Pallor (rather than flushing)
        - No respiratory difficulty nor pruritus, urticaria or angioedema

2. Acute respiratory distress:
    - Status asthmaticus
    - Epiglottitis
    - Foreign-body aspiration
    - Pulmonary embolism
    - Hereditary angioedema
        Stridor secondary to laryngeal edema, but no pruritus or urticaria.
        Slower onset,
        Usually a history of recurrent attacks or a positive family history.
        Poor response to epinephrine

3. Disorders with similar cutaneous manifestations.
    - Systemic mastocytosis: The mast cells may degranulate causing systemic effects exactly like anaphylaxis. Indeed some patients originally diagnosed as having idiopathic anaphylaxis have later been found to have systemic

mastocytosis on bone marrow biopsy. Both may have elevated plasma histamine, urinary histamine, and serum tryptase levels. Suspicion of the diagnosis should be raised with the recognition of the classic reddish brown macular-papular skin lesions with a positive Darier's sign. (urticaria pigmentosa)

- Cold urticaria. These patients can present with generalized urticaria, angioedema, laryngeal edema, and vascular collapse, resulting from a massive outpouring of histamine. The history is usually suggestive, especially if they have a positive past history of urticaria with cold stimulus. These patients are usually particularly at risk with aquatic activities, and the precipitating stimulus is frequently swimming in cold water.
- Serum sickness. May present with urticaria, but is generally not an abrupt or progressive event. Associated with fever, lymphadenopathy, and arthritis
- Carcinoid syndrome. Carcinoid symptoms may sometimes be mistaken for anaphylaxis, given the presence of flushing, tachycardia, hypotension, gastrointestinal symptoms, and bronchospasm. However, urticaria and angioedema are absent, and upper respiratory tract obstruction does not occur. Occasionally, carcinoid syndrome may have elevated 24-hour urine histamine; however they also have increased urinary levels of 5-HIAA.

Nonimmunologic Risk Factors for Severe or Fatal Anaphylaxis

- Beta-adrenergic blockade.
  - The presence of beta-adrenergic blocking drugs may increase the likelihood of anaphylaxis.
  - It definitely increases its severity and interferes with the use of epinephrine to treat anaphylaxis.
  - It acts to block the expected beta-i and beta-2 anti-anaphylactic actions of epinephrine, thus facilitating unopposed aipha-adrenergic effects, which in the presence of excess epinephrine, may constrict coronary arteries and dangerously exaggerate the systemic pressor effects of epinephrine. In addition, reflex vagotonic effects that can lead to augmented mediator release, bronchoconstriction, and bradycardia.
  - Even small amounts of the drug, such as that absorbed from Timoptic eye drops, can cause problems.
- Asthma. Asthmatic patients appear to be twice as likely to die if anaphylaxis occurs.
- Cardiac disease. Anaphylaxis is more likely to be severe or fatal in patients with congestive heart failure or arteriosclerotic coronary artery disease.
- Parenteral administration: Oral administration appears to be the safest, while the parenteral route is the most hazardous.
- Delayed anaphylaxis.

A more prolonged period between antigen exposure and onset of symptoms (latent period) has been thought to be associated with a more benign outcome; however, a recent prospective study of anaphylaxis in 25 consecutive patients by Sullivan (Dallas, Texas) suggests that patients with delayed onsets may be at greater risk of a fatal

outcome. He found that recurrent or prolonged reactions were 2.8 fold more likely if the onset was 30 or more minutes after exposure to the stimulus.

General therapeutic measures:

- Close monitoring: PFT's, oxygen saturation, cardiac monitor, serial BPs
- Initial evaluation and treatment should be directed to maintenance of an effective airway and circulatory system.
- Epinephrine: Nearly an ideal drug. It suppresses mediator release from mast cells and basophils and reverses many of the end organ effects of the mediators. It both relaxes bronchial smooth muscle and produces peripheral vasoconstriction
- Dosage: 1:1,000 concentration
  - Adult: 0.3 to 0.5 ml, SC or IM (Asthma: 0.5 ml)
  - Child: 0.01ml/kg (up to 0.3 ml), SC or IM
  - Repeat: after 10 minutes
  - Avoid: IV bolus administration (arrhythmias)
  - Caution: elderly or underlying cardiovascular or cerebrovascular disease
- If anaphylaxis from injection/sting (except head, neck, hands, feet)
  - Administer 0.1 to 0.2 ml in the injection/sting site
  - Apply a tourniquet (released 1-2 minutes every 10 minutes)
  - Remove stinger
- Intravenous infusion (1 mg diluted in 500 ml of D5W)
  - Adult: 2-4 ug/minute (1-2 mi/minute) Child: 0.1 ugfkg/minute (0.05 mI/kg/min)
- Prompt recognition and treatment is critical -- early use is the key. The longer initial therapy is delayed, the greater the incidence of fatality.

Expansion of Intravascular Volume

- Trendelenburg position
- Normal saline or Plasmanate can be administered (Child: 10-30 ml/kg)

Vasopressor infusion

- Norepinephrine (Levophed) appears to be the most consistently effective pressor in anaphylaxis
- Dopamine hydrochloride (Intropin):
  - Primarily a beta-adrenergic stimulant.
  - May be useful in the presence of cardiac failure.
- Glucagon: IV glucagon has been effective in patient on beta-blockers who are in shock and unresponsive to beta-agonists. This may reflect a direct action of glucagon on cardiac that is independent of the beta-receptor.
  (It is probably not indicated for bronchospasm).
  - Initial dose of 1-5 mg, followed by infusion of 5-15 mg/minute titrated against blood pressure.

Antihistamines

H1 antihistamines (Benadryl) Further therapy can be provided by an Hi antihistamine; **however this drug is not a substitute for epinephrine.**

- Dose: 1-2 mg/kg (Max:' 50 mg)
  IV (slowly over 5-10 minutes), IM, or P0 (depending on the severity)
- Other antihistamines (Atarax) can be substituted for oral therapy.

H2 antihistamines. (Cimetidine/Ranitidine) Although pruritus, wheal and flare reactions, and angioedema reactions are primarily Hi receptor mediated, histamine induced hypotension and cardiac arrhythmias can be mediated by both Hi and H2. receptors. Therefore, though has not been proven to be of benefit for anaphylaxis, H2 antihistamine can be added.

- Dose: 4 mg/kg Cimetidine IV (slowly over 5 minutes)
- Exception: beta-blockers. In this setting, cimetidine could decrease clearance of the beta-blocker and thus perpetuate its action.

Upper Airway Obstruction

- Epinephrine
- Oxygen
- Racemic epinephrine: 0.3 ml in 3 ml saline (or nebulized epinephrine)
- Intubation or cricothyrotomy

Lower Airway Obstruction

Managed with a stepwise approach similar to that used for severe asthma.

- Epinephrine
- Oxygen
- Nebulized beta-agonists
- Aminophylline bolus/infusion
- Endotracheal intubation

Late-phase reactions It is important to realize that some patients will resolve their anaphylaxis only to have a spontaneous recrudescence 8 to 24 hours later. This is the so-called late phase response.

- Bronchodilators prevents the early, but not the late phase.
- Corticosteroids prevents the late, but not the early phase.
- Cromolyn prevents both the early and late phase.

- The prospective study by Dr. Sullivan of anaphylaxis in 25 consecutive patients noted three distinct clinical patters:

  Uniphasic: 52%
  Biphasic: 20%
  Protracted: 28% (hypotension or respiratory distress lasting 5 to 32 hours despite aggressive therapy).

- Contrary to expectations, glucocorticoid therapy introduced during the initial phase of anaphylaxis did not prevent the appearance of recurrent or protracted anaphylaxis.

Steroids may indeed lessen the chances or decrease the intensity of a recurrence, but they cannot be relied upon to eliminate it.

- Therefore, individuals who have experienced a significant episode of anaphylaxis require at least 12 -24 hours of additional observation, and may require admission for overnight observation.

Corticosteroids

- Corticosteroids are <u>not</u> helpful in the acute management of anaphylaxis,
- In moderate or severe reactions they should be started early to modify or perhaps prevent protracted or reèurrent symptoms.
- Dosage:

  Methyiprednisolone: 2 mg/kg, followed by 1 mg/kg q 6 hours

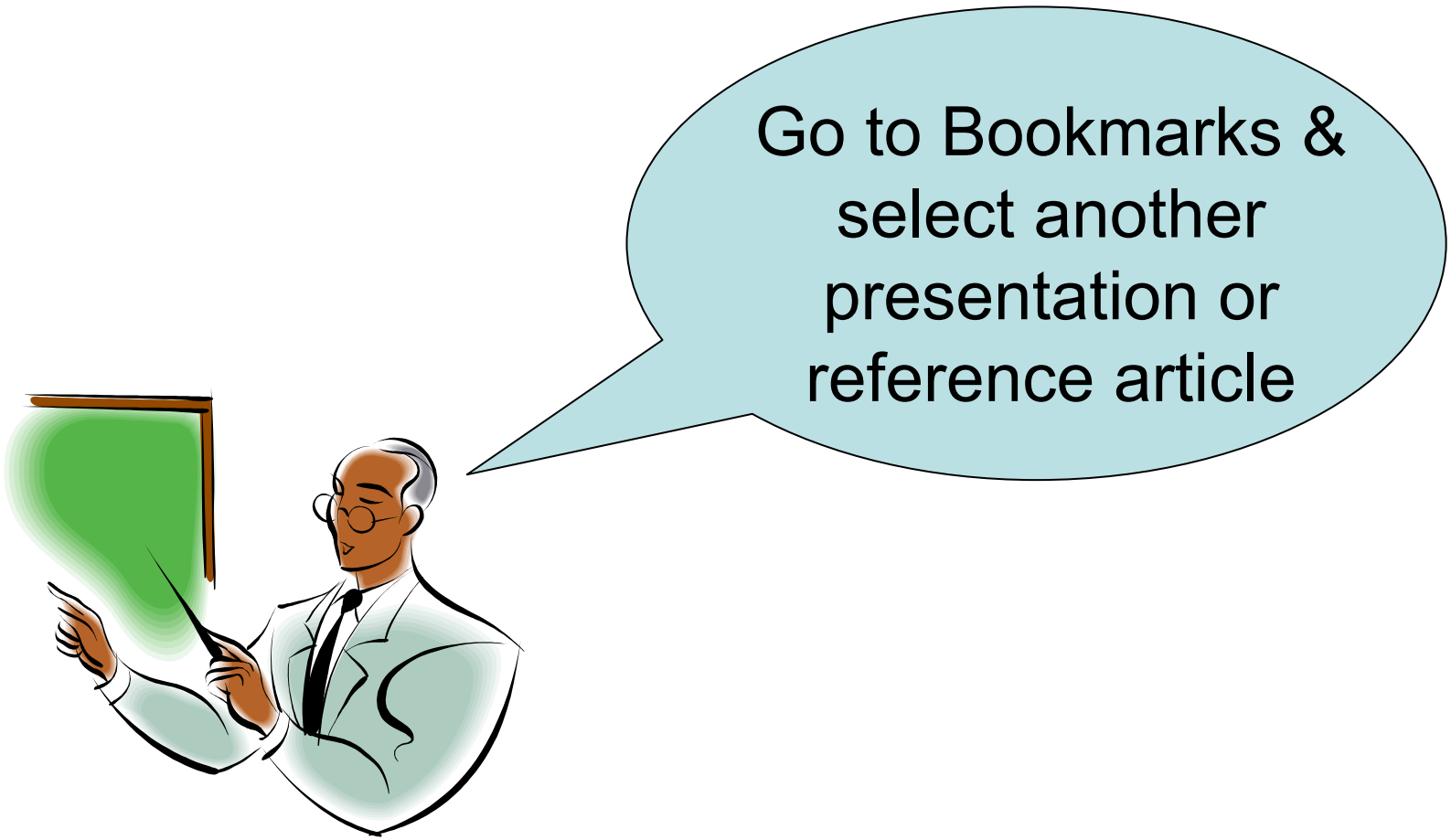
  Hydrocortisone: 10 mg/kg, followed by 5 mg/kg q 6 hours.

  (Hydrocortisone sodium succinate)

Disposition

- In the elderly patient, the patient with cardiovascular disease, and the patient with severe or protracted hypoxia: observe for myocardial ischemia and cerebrovascular complications.
- Identify the stimulus to anaphylaxis for future avoidance
  - Exercise, cold, stinging insects, drugs, and - frequently forgotten - foods
- Arrange for immunotherapy whenever possible
  - Hymenoptera: 98% effective
- Discuss desensitization (penicillin, sulfa) and premedication with corticosteroids and H1 antihistamines (radiocontrast studies)
- Medic-alert bracelet or necklace
- Continue oral prednisone and H1 antihistamines (6 to 48 hours)
- Ana-kit. Self-administered epinephrine should be provided for patients who are likely to experience anaphylaxis outside a medical facility. The patient should be taught the indications and details of self-administration.

End of Selection



SYSTEMIC ANAPHYLAXIS

ALEXANDRA S. WOROBEC, M.D.
DEAN D. METCALFE, M.D.

Systemic anaphylaxis is an acute allergic reaction involving the release of mediators from mast cells, basophils, and secondarily recruited inflammatory cells, which may occur within a few minutes to a few hours following exposure to a triggering agent. Literally meaning "anti-protection" from the Greek "ana" = no and "phylaxis" = protection, anaphylaxis is potentially life threatening and therefore constitutes a medical emergency that requires prompt recognition and therapy.

Anaphylactic reactions have been classically divided into two categories based on mechanism: (1) anaphylaxis that is traditionally considered to involve IgE, mast cells, and basophils; and (2) anaphylactoid reactions that may be due to other immunologic as well as nonimmunologic mechanisms. Recent murine work using an IgE knockout model is consistent with the hypothesis that non–IgE-mediated signal pathways may also initiate a systemic reaction resembling anaphylaxis. A representative list of etiologic agents involved in anaphylactic syndromes classified according to possible mechanism is included in Table 1. Nonetheless, these distinctions remain a matter of semantics since clinical symptomatology and treatment of all categories is essentially the same.

The signs and symptoms of anaphylaxis may be isolated to one or involve several organ systems. Cutaneous manifestations include erythema, flushing, pruritus, urticaria, and angioedema. Gastrointestinal symptoms include crampy abdominal pain, nausea, vomiting, and diarrhea. Uterine cramping may occur. Life-threatening manifestations most commonly involve respiratory distress secondary to upper airway obstruction from angioedema of the tongue, oropharynx, or larynx, or secondary to lower airway obstruction from bronchospasm. Cardiovascular symptoms are often severe and refractory and include hypotension, arrythmias, and hypovolemic shock. Involvement of the cardiovascular system constitutes the second most common cause of death in anaphylactic syndromes. In general, the magnitude of the anaphylactic response parallels the magnitude of the stimulus, with more severe reactions occurring closer temporally to the time of exposure to the inciting agent.

RECOGNITION AND TREATMENT OF ANAPHYLAXIS

Treatment of anaphylaxis requires early recognition of clinical symptoms associated with the syndrome and a history of possible antigen exposure. Several disorders may present with clinical manifestations not unlike anaphylaxis and hence, comprise the differential diagnostic list for this syndrome (Table 2). The vasovagal reaction is perhaps the most common diagnosis which is confused with anaphylaxis. It presents with symptoms of pallor, profuse sweating, weakness, bradycardia, hypotension, and occassionally syncope. Because bradycardia is an early manifestation of hypovolemic shock, heart rate cannot be used reliably to differentiate a vasovagal reaction from anaphylaxis. Indeed, the heart rate has been reported to be low, normal, or elevated during anaphylaxis. Elevated plasma histamine or tryptase levels, particularly the latter, are retrospective supportive findings in favor of a mast cell–mediated disorder such as anaphylaxis.

The immediate treatment of anaphylaxis begins with a rapid assessment of the patient's level of consciousness, along with the patient's airway, breathing, and circulation (ABCs). A broad outline of measures to be instituted in a patient with probable anaphylaxis is presented in Table 3. The management of anaphylaxis must take into consideration the severity of the reaction.

The first-line drug of choice for treating anaphylaxis is subcutaneous epinephrine. The dose of epinephrine injected subcutaneously is usually 0.3 ml of 1:1,000

Table 1 Classification of Anaphylactic Syndromes

Mechanism	*Etiologic Agents**
I. IgE Mediated	
Haptens	Most antibiotics: penicillins, cephalosporins, sulfonamides, tetracycline, bacitracin, nitrofurantoin, amphotericin
	Industrial chemicals: ethylene oxide, glue, formaldehyde
Complete Antigens	Allergen extracts: pollens, molds, danders
	Venoms: hymenoptera (including fire ant), snake, deer fly (Chrysops species), kissing bug (Triatoma species)
	Foreign proteins: chymopapain, horse serum
	Foods: peanut, milk, egg, seafood, grains, tree nuts
	Vaccines contaminated with egg protein: influenza
	Human proteins: insulin, vasopressin, serum, and seminal proteins
	Enzymes: streptokinase, trypsin, L-asparaginase
	Protamine
	Latex
	Immunomodulators: cyclosporine
	Ruptured hydatid cyst
II. Direct Mast-Cell Activation	Hypertonic solutions: radiocontrast media, mannitol
	Opiates
	Polysaccharides: Acacia, dextran, iron-dextran
	Muscle depolarizing agents: curare, d-tubocurarine
	Polymyxin B, vancomycin
	Some chemotherapeutic agents
III. Complement Mediated: C3a, C5a	Human proteins: immunoglobulins, plasma
	Dialysis membranes
IV. Arachidonic Cascade Mediated	Nonsteroidal anti-inflammatory agents, aspirin
V. Mechanism Unknown	
Exercise-induced anaphylaxis	
Idiopathic recurrent anaphylaxis	
Cholinergic urticaria with anaphylaxis	
Cold-induced urticaria with anaphylaxis	
Steroid preparations	Progesterone, hydrocortisone
Mastocytosis	
Sulfites	

*Examples only, list is not complete.

Table 2 Differential Diagnosis of Anaphylaxis

Pulmonary
- Laryngeal edema
- Epiglottitis
- Foreign body aspiration
- Pulmonary embolus
- Asphyxiation
- Hyperventilation

Cardiovascular
- Myocardial infarction
- Arrhythmia
- Hypovolemic shock
- Cardiac arrest

CNS
- Vasovagal reaction
- Cerebrovascular accident
- Seizure disorder
- Drug overdose

Endocrine
- Hypoglycemia
- Pheochromocytoma
- Carcinoid syndrome
- Catamenial (progesterone-induced) anaphylaxis

Psychiatric
- Vocal cord dysfunction syndrome
- Munchausen's disease
- Panic attack/Globus hystericus

Other
- Hereditary angioedema
- Cold urticaria
- Idiopathic urticaria
- Mastocytosis
- Serum sickness
- Idiopathic capillary leak syndrome
- Sulfite exposure
- Scombroid poisoning (tuna, blue-fish, mackeral)

aqueous epinephrine in the adult, although the dosage may need to be decreased in the elderly (to say, 0.2 ml) or increased in patients receiving beta-adrenergic blockers (to 0.5 ml). Dosing of epinephrine in children is based on weight, or 0.01 ml per kilogram of a 1:1,000 dilution up to a maximum of 0.3 ml of epinephrine injected subcutaneously. A second epinephrine injection (0.1 to 0.2 ml of 1:1,000 epinephrine) may be given into the site of an insect sting, or drug or allergen injection site to delay systemic absorption of the agent if the antigen source is not a digit or other terminal region of the anatomy.

The 1993 report of the Working Group on Asthma in Pregnancy with the National Heart, Lung and Blood Institute (NIH publication #93–3279) considering the treatment of pregnant women with epinephrine (and likewise diphenhydramine) listed epinephrine as the initial pharmacologic agent of choice in the management of anaphylaxis. A second-line agent of choice for some obstetricians for the treatment of hypotension secondary to anaphylaxis in the pregnant patient is ephedrine, 10 to 15 mg, administered IV push. Although less effective than epinephrine, it is believed that its predominant beta-adrenergic activity may cause less reduction in uterine blood flow than epinephrine.

Along with the administration of epinephrine to increase systemic vascular resistance and elevate diastolic pressure, produce bronchodilation, and increase inotropic and chronotropic cardiac activity, additional measures may be required to stabilize and maintain

Table 3 Step-Wise Treatment of Systemic Anaphylaxis: General Measures*

NOTE: To be performed at the time of administration of the first dose(s) of epinephrine SC

1. Removal or discontinuation of inciting agent
   Special case for insect sting or allergen injection:
   Application of a loose tourniquet proximally if an allergen, injection, or sting is on an extremity with further loosening of the tourniquet q15min. The insect stinger should be gently flicked off. 0.1-0.3 ml of aqueous epinephrine may be administered SC at the site of antigen injection to delay its absorption
2. Examination of skin color, upper and lower airway patency. Secure and maintain adequate airway
3. Monitoring of vital signs: BP, pulse, respiratory rate
4. Monitoring of patient's level of consciousness
5. Placement of patient in Trendelenburg position as appropriate
6. High flow supplemental oxygen (100%) with pulse oximetry monitoring
   Dose: 4-10 L/min via a non-rebreather mask such as the Venturi
   Intubation and mechanical assistance indicated when the $Paco_2$ is greater than or equal to 65 mm Hg
7. Insertion of a short, large bore peripheral IV line as appropriate for age with administration of fluids
   IV fluids: **a. Initial recommendation:**
   Crystalloid solutions:
   1. 0.9% normal saline or
   2. Lactated ringer's solution

   Monitor vital signs, pulmonary status, and urine output
   Keep SBP greater than or equal to 90 mm Hg
   This may require up to 1 L q15-30min in an adult or 20-30 ml/kg/hr in the pediatric age group for the first several hours

   b. Severe or persistent hypotension:
   Colloid solutions:
   i. Dextran—available in 2 forms:
      1. Dextran 70 (6% solution)
      2. Dextran 40 (10% solution)
   ii. Hetastarch (Hespan)
   iii. Serum Albumin—available in 2 concentrations:
      1. 5% solution: effective plasma expander
      2. 25% solution: more potent elevator of plasma oncotic pressure
8. For severe or refractory hypotension:
   a. Also consider use of antishock trousers to increase afterload. (Note: controversial efficacy in the treatment of peripheral shock)
   b. Lack of efficacy of measures discussed in steps one to seven above, including fluid resuscitation may mandate use of inotropic agents. By this stage, a central line to determine central venous pressure and/or Swan-Ganz catheter insertion is recommended. For unresponsive hypotension due to myocardial depression, an intra-aortic balloon counterpulsation pump may be considered
9. Observation in a monitored setting (i.e., ICU) for at least 24 hours after a moderate-severe anaphylactic reaction; for at least 8-12 hours after a mild reaction

*Exclusive of drug treatment, which is presented in Tables 4 and 5.

oxygenation and cardiac output. Other medications may be administered to supplement the effect of epinephrine. Clinical and experimental evidence suggests that treatment with a combination of H_1- and H_2-receptor antagonists such as diphenhydramine and ranitidine may be more effective than treatment with an H_1-antihistamine alone in preventing histamine-induced hypotension. Patients with severe anaphylaxis or those who have received systemic corticosteroid therapy within the previous 6 months should receive pharmacologic doses of parenteral glucocorticoids given the low but discernible frequency of biphasic and protracted anaphylactic reactions.

For respiratory involvement, patients must be managed aggressively with nebulized and parenteral agents (Tables 4 and 5). Most commonly, nebulized beta-adrenergic agonists are administered for bronchospasm, with nebulized epinephrine or racemic epinephrine given for upper airway edema. Supplemental oxygen should always be administered in the highest concentration possible, with serial arterial blood gas analyses performed to maintain oxygen saturation greater than or equal to 90 percent ($Po_2 < 60$ mm Hg, $Pco_2 > 65$ mm Hg). In recalcitrant cases, endotracheal intubation, cricothyroid membrane puncture (avoid this procedure in children younger than 10 years of age), or tracheostomy may be necessary to ensure adequate airflow.

Hypotension is generally managed initially via administration of crystalloid solutions (Table 3) such as 0.9 percent normal saline or lactated Ringer's solution through a large bore intravenous line at a rate depending on the degree of hypovolemia, status of the vital signs, pulmonary exam, and urine output. The goal of treatment is to maintain the systolic blood pressure (SBP) greater than or equal to 90 mm Hg. Because these isotonic solutions contain small molecules that rapidly escape from the vascular space into the interstitium, their volume expansion effects are short-lived. Nonetheless, crystalloids offer the advantage of being nonallergenic and virus free and having no potential to produce a hypotensive reaction.

Refractory hypotension or frank shock in a patient with anaphylaxis warrants a two fold approach to therapy. First, central venous access should be established for monitoring of the central venous pressure and possible need for Swan-Ganz catheter placement and monitoring of cardiac output and the pulmonary capillary wedge pressure. Concomitantly, colloids or solutions

Table 4 Step-Wise Treatment of Systemic Anaphylaxis: Pharmacologic Therapy in Adults

Medication	*Route*	*Dosage*	*Complications*
A. Indicated for all reactions (urticaria, angioedema, bronchospasm, laryngeal edema, and systemic symptoms)			
1. Epinephrine (drug of first choice)	SC	0.3 ml of a 1:1,000 dilution (usual range 0.2-0.5 ml) q10-15min × 3 doses, if necessary	Tachycardia, tremor, anxiety, arrhythmias
	IM	0.3 ml of a 1:1,000 dilution q10-15 min **(pregnant patient)**	
2. Ephedrine	IV push	10-25 mg **(only to be considered in the pregnant patient)**	
3. Antihistamines			
H_1-Blockers:			
Diphenhydramine	IM or IV	50-75 mg q6h Drip may afford better control of sxs: 5 mg/kg/24h	Large doses: anticholinergic effects, may depress respiration
H_2-Blockers:			
Ranitidine	PO (mild sxs)	150 mg q8-12h	
	IV	50 mg q6-8h	
Cimetidine	PO (mild sxs)	300 mg q6-8h	*Note:* cimetidine is not compatible with IV aminophylline
	IV	300 mg q6-8h	
Famotidine	IV	20 mg q12h	
B. Indicated for laryngeal edema			
1. Epinephrine	Nebulized	1% solution of 1:100 epinephrine via hand bulb nebulizer, 1-3 deep inhalations q3h	
2. Racemic epinephrine	Nebulized	2.25% solution of 1:100 racemic epinephrine via hand bulb nebulizer, 1-3 deep inhalations q3h	*Note:* racemic epinephrine has approximately half the activity of epinephrine
C. Indicated for bronchospasm			Nausea, vomiting, arrhythmias
1. Beta-adrenergic bronchodilators:			
Albuterol	Nebulized	2.5-5.0 mg (0.5 ml of 0.5% solution diluted to a final volume of 3 ml with 0.9% NS) given over 5-15 min. each dose, q20min × 6 doses maximum	
Metaproterenol	Nebulized	0.3 ml of 5% solution diluted in 2.5 ml of 0.45% or 0.9% NS, given over 5-15 min each dose, q4h	
Terbutaline	Metered	400 μg or 2 inhalations (200 μg/metered spray), q4-6h	
2. Steroids:			
Methylprednisolone	IV	60-80 mg × 1 dose, followed by prednisone 60 mg PO q.d. × 2d	*Note:* steroids have no antianaphylactic actions and do not alleviate immediate acute, life-threatening manifestations
Hydrocortisone	IV	100-200 mg q6-8h (up to 5-10 mg/kg q6-8h)	
Prednisone	PO (mild rxns)	20-40 mg q.d. with quick taper	
3. Aminophylline (second-line therapy)	IV	5-6 mg/kg in 20 ml D_5W over 10-15 min (loading dose), 0.5-1.0 mg/kg/h (maintenance dose)	Nausea, vomiting, seizures, arrhythmias

Continued.

containing large macromolecular polymers should be administered intravenously. These solutions allow a greater increase in the plasma oncotic pressure via attraction of water from the interstitium, thereby actually producing intravascular volume expansion in an increment above that which is administered. Example colloid solutions are dextran, hetastarch (Hespan), and serum albumin. Dextran solutions are available in two forms—a high molecular weight form (dextran 70, 6 percent solution) and a low molecular weight form (dextran 40, 10 percent solution)—which have intravascular half-lives of 2 to 3 days and 12 to 18 hours, respectively. Disadvantages of dextran administration include the potential for anaphylaxis and a bleeding diathesis, along with agglutination of red blood cells, thus making subsequent blood cross-matching difficult or impossible. Hetastarch (Hespan), an artificial polymer with a M_r 450 kD, displays a long-lasting volume expansion effect of 24 to 36 hours, is relatively nonallergenic, and doesn't interfere with blood typing and cross-matching. Disadvantages include alteration of the coagulation function. Serum albumin, available in a 5 percent and 25 percent solution, is the most commonly used plasma expander, but it is expensive and occasion-

Table 4 Step-Wise Treatment of Systemic Anaphylaxis: Pharmacologic Therapy in Adults—cont'd

Medication	*Route*	*Dosage*	*Complications*
D. Indicated for cardiovascular collapse (refractory hypotension, shock)			
1. Epinephrine (initial therapy)	Via ETT	1 mg = 10 ml of a 1:10,000 dilution in 5 ml 0.9% NS, given via a long needle or catheter into an ETT, followed by hyperventilation	*Note:* given when response to SC Epi is too slow or adequate vascular access has not been obtained yet
	IV push	0.1-0.2 ml of 1:1,000 dilution in 10 ml 0.9% NS, given over 5'. This may require follow-up administration of an epinephrine IV drip	
	IV drip	0.1 μg/kg/min, use 1 ml of 1:1,000 dilution in 250 ml D_5W (4 μg/ml) at 1 μg/min, increasing to a maximum of 4-10 μg/min	
2. Dopamine	IV drip	2-20 μg/kg/min (2 amps = 400 mg in 500 ml D_5W)	Arrhythmias
3. Dobutamine	IV drip	2-30 μg/kg/min (2 amps = 500 mg in 500 ml D_5W)	Arrhythmias, esp. tachycardia
4. Norepinephrine	IV drip	0.5-1.0 μg/min (initial dose), followed by 2-12 μg/min	Arrhythmias
5. Amrinone	IV drip	0.75 mg/kg IV bolus over 2-3 min, then 2-15 μg/kg/min (maintenance)	
E. Indicated for patients on beta-blockers with refractory shock			
1. Glucagon (first-line therapy)	IV push	1-5 mg over 2-5 minutes IV push	Nausea, vomiting
	IV drip	1 mg in 1 L D_5W at 5-15 μg/min	
2. Isoproterenol	IV drip	2-10 μg/min, start with 0.1 μg/kg/min (1 mg in 500 ml D_5W), doubling dose q15'	Tachycardia, arrhythmias

D_5W, 5% glucose in distilled water; *ETT,* endotracheal tube; *NS,* normal saline; *rxns,* reactions; *sxs,* symptoms.

ally associated with increased pulmonary interstitial edema.

In addition to fluid resuscitative measures, treatment of refractory hypotension and shock may require pharmacologic intervention. Replacement of serial subcutaneous or intramuscular epinephrine injections with an intravenous bolus, followed by a continuous intravenous 1:10,000 epinephrine drip, is generally recommended as first-line therapy. Lack of response to this measure may warrant addition of an intravenous continuous infusion of dopamine or dobutamine, depending on the patient's underlying cardiovascular status, followed by norepinephrine or amrinone. Patients on maintenance beta-blocker therapy may be relatively resistant to epinephrine; in these patients intravenous glucagon should be considered as a treatment for refractory hypotension, followed by isoproterenol. Established dosages of these vasoactive inotropic medications (Tables 4 and 5) are as provided by the American Heart Association (AHA) guidelines. Patients receiving any of these agents must be monitored for development of anginal symptoms and possible arrythmias in an intensive care unit setting, with both reactions being treated according to AHA guidelines with the appropriate agent. Hypertension resulting from unopposed beta-adrenergic and alpha-adrenergic activity may require prompt treatment with nitroprusside (initial dose: 10 μg per minute IV, increasing by 10 μg per minute IV every 4 minutes to 10 to 20 mg per minute IV until BP stabilizes) or phentolamine (initial dose: 0.5 mg per minute IV to a maximum of 10 mg IV, maintenance dose: 25 to 50 mg IV every 3 to 6 hours). Even with close cardiac monitoring and titration, myocardial infarction is a known associated sequelae of systemic anaphylaxis, either from the initial hypotensive insult to the myocardium or from alpha- and/or beta-adrenergic effects on an already compromised cardiovascular system.

Patients with a mild to moderate anaphylactic reaction should have their vital signs and cardiac and respiratory status monitored for at least an additional 8 to 12 hours after clinical signs and symptoms of anaphylaxis abate. For moderate reactions (i.e., bronchospasm, generalized urticaria) antihistamines and steroids may be continued for several days after the initial reaction, and the patient may be given a self-injectable epinephrine device (EpiPen or Ana-Kit) with a prescription for refills and counseled in its proper use before being discharged. Patients with severe reactions may require monitoring for a minimum of 24 hours after stabilization and warrant close outpatient follow-up and allergy evaluation.

PREVENTION AND PROPHYLAXIS

Basic principles in the prevention of anaphylaxis in high-risk individuals are outlined in Table 6. Identification and avoidance of causative agents, if feasible,

Table 5 Step-Wise Treatment of Systemic Anaphylaxis: Pharmacologic Therapy in Children

Medication	*Route*	*Dose*	*Complications*
A. Indicated for all reactions (urticaria, angioedema, bronchospasm, laryngeal edema, and systemic symptoms)			
1. Epinephrine (drug of first choice)	SC	0.01 mg/kg of a 1:1,000 dilution, up to 0.3 ml q10-15min	Tachycardia, tremor, anxiety, arrhythmias
2. Antihistamines			
H_1-Blockers:			
Diphenhydramine	IM or IV	1-2 mg/kg q6h Drip may afford better control of sxs: 5 mg/kg/24h	Large doses: anticholinergic effects, may depress respiration
H_2-Blockers:			
Ranitidine	IV	12.5-50 mg q6-8h	
B. Indicated for laryngeal edema			
1. Epinephrine	Nebulized	For use only in children >4 yrs of age: 1% solution of 1:100 epinephrine via hand bulb nebulizer, 1-3 deep inhalations q3h	
2. Racemic epinephrine	Nebulized	For use only in children >4 yrs of age: 2.25% solution of 1:100 racemic epinephrine via hand bulb nebulizer, 1-3 deep inhalations q3h	*Note:* racemic epinephrine has approximately half the activity of epinephrine
C. Indicated for bronchospasm			
1. Beta-adrenergic bronchodilators:			Nausea, vomiting, arrhythmias
Albuterol	Nebulized	For use only in children >5 yrs of age: 2.5-5.0 mg (0.5 ml of 0.5% solution diluted to a final volume of 3 ml with 0.9% NS) given over 5-15 min each dose, q20min × 6 doses maximum For use in children <5 yrs of age: 1.2-2.5 mg given over 5-15 min each dose, q20min × 6 doses maximum	
Metaproterenol	Nebulized	For use only in children >12 yrs of age: 0.3 ml of 5% solution diluted in 2.5 ml of 0.45% or 0.9% NS, given over 5-15 min each dose, q4h For use in children between 6-12 yrs of age: 0.1 ml of 5% solution diluted in 0.9% NS to a final volume of 3.0 ml, given over 5-15 min each dose, q4h	
Terbutaline	Metered dose inhaler	For use only in children >12 yrs of age: 400 μg or 2 inhalations (200 μg/metered spray), q4-6h	
2. Steroids:			
Methylprednisolone	IV	0.5 mg/kg/24 hr in divided doses	*Note:* same effects as listed in Table 4
Hydrocortisone	IV	4-8 mg/kg q6-8h	
3. Aminophylline (second-line therapy)	IV	5-6 mg/kg in 20 ml D_5W over 10-15 min (loading dose), 0.5-1.0 mg/kg/hr (maintenance dose)	Nausea, vomiting, seizures, arrhythmias

Continued.

remains the most important step in the management of susceptible individuals. Patients should be taught to recognize the clinical signs of impending anaphylaxis (i.e., lump in the throat with difficulty breathing, lightheadedness, feeling of impending doom) and feel comfortable and skilled in the technique of self-administration of subcutaneous epinephrine. An epinephrine autoinjector device should be carried by the patient at all times, with several spares in convenient locations (home, work) and these should be renewed on a yearly basis.

Patients with idiopathic anaphylaxis who experience more frequent attacks should be placed on maintenance therapy with oral antihistamines and perhaps, steroids (i.e., oral prednisone 20 to 40 mg daily), until the episodes abate, with tapering of steroids thereafter. High-risk patients on beta-blocker therapy, including topical medications used in the treatment of glaucoma,

Table 5 Step-Wise Treatment of Systemic Anaphylaxis: Pharmacologic Therapy in Children—cont'd

Medication	*Route*	*Dose*	*Complications*
D. Indicated for cardiovascular collapse (refractory hypotension, shock)			
1. Epinephrine (initial therapy)	Via ETT	0.1 mg/kg of a 1:10,000 dilution in 5 ml 0.9% NS, given via a long needle or catheter into an ETT, followed by hyperventilation	*Note:* given when response to SC Epi is too slow or adequate vascular access has not been obtained yet
	IV drip	0.1 μg/kg/min (use 0.5 mg of a 1:1,000 dilution of epinephrine in 100 ml 0.9% NS to produce a concentration of 5.0 μg/ml)	
2. Dopamine	IV drip	2-20 μg/kg/min (2 amps = 400 mg in 500 ml D_5W)	Arrhythmias
3. Dobutamine	IV drip	2-30 μg/kg/min (2 amps = 500 mg in 500 ml D_5W)	Arrhythmias, esp. tachycardia
4. Norepinephrine	IV drip	0.5-1.0 μg/min (starting dose), followed by 2-12 μg/min (maintenance dose)	Arrhythmias
E. Indicated for patients on beta-blockers with refractory shock*			
1. Glucagon (first-line therapy)	IV push	1-5 mg over 2-5 minutes, IV push	Nausea, vomiting
2. Isoproterenol	IV drip	2-10 μg/min. Start with 0.1 μg/kg/min (1 mg in 500 ml D_5W), doubling dose q15min	Tachycardia, arrhythmias

D_5W, 5% glucose in distilled water; *ETT*, endotracheal tube; *NS*, normal saline; *sxs*, symptoms.
*Beta-blockers less commonly used in children than adults.

Table 6 Strategies to Prevent or Lessen the Severity of Anaphylactic Reactions

I. General Principles:
- A. Obtain accurate and complete patient medical history. Skin tests or RAST are valuable in identifying individuals at risk for anaphylaxis from agents such as penicillin and insect venoms
- B. Patient avoidance of allergens known to precipitate anaphylaxis
- C. Medic-Alert bracelet should be worn by at-risk patients at all times
- D. Patients at risk should carry an Epi Pen or Ana-Kit at all times and be properly skilled in its correct use
  - Adults: 0.3 ml of 1:1,000 dilution of Epinephrine (Epi Pen)
  - Pediatric: 0.15 ml of 1:1,000 dilution of Epinephrine (Epi Pen Jr.)
- E. Desensitization may be recommended for patients with Hymenoptera sensitivity
- F. Require a clear indication for drug use. Consider desensitization by oral route
- G. Desensitize patients to any drug known to have caused anaphylaxis if urgently required to treat a life-threatening disease. Prefer oral desensitization, if feasible
- H. Avoid use of beta-blockers, NSAIDs, or aspirin or replace with reasonable alternatives

II. Prophylaxis of Exercise-Induced Anaphylaxis:
- A. Avoid food ingestion for approximately 6 hours before exercise
- B. Avoid intake of NSAIDs or ASA
- C. In general, prophylactic antihistamines (H_1- and H_2-receptor antagonists) and cromolyn are ineffective

III. Prophylaxis (Desensitization procedures, necessary administration of agent known to cause anaphylaxis):
- A. Pretreatment with an H_1-receptor and possibly H_2-receptor antagonist 12 to 24 hr before administration of agent known to cause anaphylaxis
  1. H_1-blocker: **diphenhydramine IV** 5 mg/kg/24 hr **(adult + pediatric)** in divided doses q6h (25-75 mg IV q6h)
  2. H_2-receptor blocker: **ranitidine IV** 1-2 mg/kg/24 hr **(adult + pediatric)** in divided doses q6-8h or **cimetidine IV** 20-40 mg/kg/24 hr **(adult + pediatric)** in divided doses q6-8h
- B. Pretreatment with steroids. **Hydrocortisone 100 mg PO or I.V.** q.d., q8h **(adult)**
- C. Avoid use of beta-blockers
- D. Continue above medications for the duration of the administration of the inciting agent

IV. Radiocontrast Allergy Prophylaxis (Adults):
- A. Switch to low osmolar nonionic contrast agents when possible
- B. Administer steroids before scheduled test:
  1. **Prednisone: 30-50 mg PO q6-8h** (i.e. 13, 7, and 1 hour prior to the study)
  2. **Methylprednisolone: 32 mg PO 12 and 2 hr before study**
- C. H_1-receptor antagonists: **Diphenhydramine: 50 mg PO 7 hr and 1 hr, or 50 mg IM 1 hr before study**
- D. H_2-receptor antagonists: **Ranitidine: 150 mg PO 7 hr and 1 hr, or 50 mg IM 1 hr before study**
- E. **Ephedrine: 25 mg PO 1 hr before study**

should be continued on these medications only if feasible alternatives are unavailable and the drug is medically indicated.

Short-term desensitization to agents such as penicillin or beta-lactam antibiotics, insulin, antithymocyte globulin, or aspirin should be performed if clearly indicated, and then so in a closely monitored setting such as an intensive care unit. Patients may be considered for premedication with H_1- and H_2-antihistamines and steroids. Because this procedure constitutes a form of "controlled anaphylaxis," patients will likely require repeat desensitization in the event of a future requirement for re-administration of the known agent. Immunotherapy is often efficacious and indicated for the prevention of Hymenoptera hypersensitivity.

Radiocontrast allergy, usually due to high osmolar ionic contrast agents, may be significantly decreased via the use of nonionic contrast agents. Pretreatment with oral steroids such as prednisone or methylprednisolone, an H_1-antihistamine such as diphenhydramine, and possibly an H_2-antihistamine such as ranitidine (with or without ephedrine) at least 2 hours before administration of radiocontrast media has been shown to decrease the risk of fatal anaphylaxis.

SUGGESTED READING

AAAI. Position statement: The use of epinephrine in the treatment of anaphylaxis. J Allergy Clin Immunol 1994; 94:666–668.

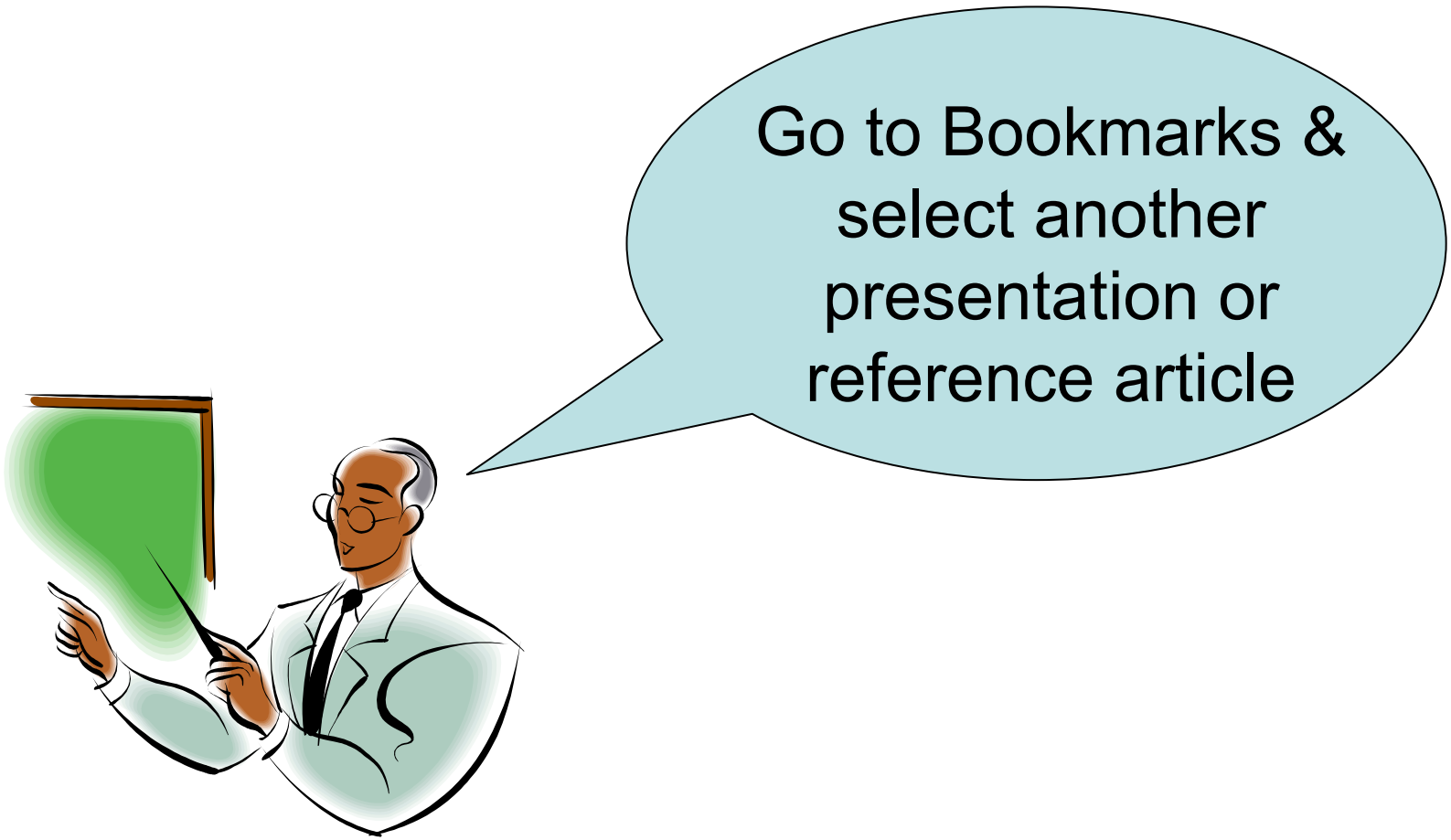
Cummins RO. Hypotension/shock/acute pulmonary edema. In: Textbook of advanced cardiac life support. Dallas: American Heart Association 1994;1.40–1.47.

Metcalfe DD. Acute anaphylaxis and urticaria in children and adults. In: Schocket AL, ed. Clinical management of urticaria and anaphylaxis. New York: Marcel Dekker, 1992;1–20.

Saryan JA, O'Loughlin JM. Anaphylaxis in children. Pediatr Ann 1992; 21:590–598.

Schatz M, Zeiger RS. Management of asthma, rhinitis, and anaphylaxis during pregnancy. Curr Obstet Gynecol 1991;1:65.

End of Selection



The diagnosis and management of anaphylaxis: An updated practice parameter

Chief Editors: **Phillip Lieberman, MD, Stephen F. Kemp, MD, John Oppenheimer, MD, David M. Lang, MD, I. Leonard Bernstein, MD, and Richard A. Nicklas, MD***

Workgroup Contributors: **John A. Anderson, MD, David I. Bernstein, MD, Jonathan A. Bernstein, MD, Jordan N. Fink, MD, Paul A. Greenberger, MD, Dennis K. Ledford, MD, James Li, MD, PhD, Albert L. Sheffer, MD, Roland Solensky, MD, and Bruce L. Wolf, MD**

Task Force Reviewers: **Joann Blessing-Moore, MD, David A. Khan, MD, Rufus E. Lee, MD, Jay M. Portnoy, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, and Stephen A. Tilles, MD**

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing "The diagnosis and management of anaphylaxis: an updated practice parameter." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients.

Published practice parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76: 282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.

*This parameter was edited by Dr Nicklas in his private capacity and not in his capacity as a medical officer with the Food and Drug Administration. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

Disclosure of potential conflict of interest: P. Lieberman—none disclosed. S. F. Kemp has consultant arrangements with MedPointe Pharmaceuticals. J. Oppenheimer—none disclosed. D. M. Lang—none disclosed. I. L. Bernstein—none disclosed. R. A. Nicklas—none disclosed. J. A. Anderson—none disclosed. D. I. Bernstein—none disclosed. J. Bernstein is on the Speakers' Bureau for Merck, GlaxoSmithKline, AstraZeneca, Aventis, Medpointe, Pfizer, Schering-Plough, and IVAX. J. N. Fink—none disclosed. P. A. Greenberger—none disclosed. D. K. Ledford—none disclosed. J. Li—none disclosed. A. L. Sheffer—none disclosed. R. Solensky—none disclosed. B. L. Wolf—none disclosed. J. Blessing-Moore—none disclosed. D. A. Khan has consultant arrangements with Pfizer; receives grants/research support from AstraZeneca; and is on the Speakers' Bureau for Pfizer, Merck, Aventis, and GlaxoSmithKline. R. E. Lee—none disclosed. J. M. Portnoy—none disclosed. D. E. Schuller is on the Speakers' Bureau for Boehringer-Ingelheim. S.L. Spector has had consultant arrangements with, has received grants/research support from, and has been on the Speakers' Bureau for Abbott, Allen & Hanburys, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Fisons, Forest, ICN, Key, Eli-Lilly, 3M, Miles, Muro, Pfizer, Purdue Frederick, Schering-Plough, Wallace, and Witby. S. A. Tilles—none disclosed.

Reprint requests: Joint Council of Allergy, Asthma & Immunology, 50 N Brockway St, #3-3, Palatine, IL 60067.

J Allergy Clin Immunol 2005;115:S483-523.
0091-6749/$30.00

doi:10.1016/j.jaci.2005.01.010

9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl) S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl):S665-S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: Part I. Ann Allergy 2003;91:105-114.
15. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 114;4:869-86.

These parameters are also available on the Internet at http://www.jcaai.org.

CONTRIBUTORS

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

CHIEF EDITORS

Phillip Lieberman, MD
Departments of Medicine and Pediatrics
University of Tennessee
College of Medicine
Memphis, Tennessee
Stephen F. Kemp, MD
Departments of Medicine and Pediatrics
University of Mississippi Medical Center
Jackson, Mississippi
John Oppenheimer, MD
Department of Internal Medicine
New Jersey Medical School
Pulmonary and Allergy Associates
Morristown, New Jersey
David M. Lang, MD
Allergy/Immunology Section
Division of Medicine
Director, Allergy and Immunology Fellowship Training Program
Cleveland Clinic Foundation
Cleveland, Ohio
I. Leonard Bernstein, MD
Departments of Medicine and Environmental Health
University of Cincinnati College of Medicine
Cincinnati, Ohio
Richard A. Nicklas, MD
Department of Medicine
George Washington Medical Center
Washington, DC

WORKGROUP CONTRIBUTORS

John Anderson, MD
Aspen Medical Center
Fort Collins, Colorado
David I. Bernstein, MD
Department of Clinical Medicine
Division of Immunology
University of Cincinnati College of Medicine
Cincinnati, Ohio
Jonathan A. Bernstein, MD
University of Cincinnati College of Medicine
Department of Internal Medicine
Division of Immunology/Allergy Section
Cincinnati, Ohio
Jordan N. Fink, MD
Allergy-Immunology
Departments of Pediatrics and Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin
Paul A. Greenberger, MD
Division of Allergy and Immunology
Northwestern University Feinberg School of Medicine
Chicago, Illinois
Dennis K. Ledford, MD
Department of Medicine
University of South Florida College of Medicine and the James A. Haley V.A. Hospital
Tampa, Florida
James T. Li, MD, PhD
Mayo Clinic
Rochester, Minnesota
Albert L. Sheffer, MD
Brigham and Women's Hospital
Boston, Massachusetts
Roland Solensky, MD
The Corvallis Clinic
Corvallis, Oregon
Bruce L. Wolf, MD
Vanderbilt University
Nashville, Tennessee

TASK FORCE REVIEWERS

Joann Blessing-Moore, MD
Department of Immunology
Stanford University Medical Center
Palo Alto, California
David A. Khan, MD
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

The diagnosis and management of anaphylaxis: An updated practice parameter

Rufus E. Lee, MD
Private Practice
Dothan, Alabama
Jay M. Portnoy, MD
Section of Allergy, Asthma & Immunology
The Children's Mercy Hospital
Professor of Pediatrics
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri
Diane E. Schuller, MD
Department of Pediatrics
Pennsylvania State University Milton S. Hershey Medical College
Hershey, Pennsylvania
Sheldon L. Spector, MD
Department of Medicine
UCLA School of Medicine
Los Angeles, California
Stephen A. Tilles, MD
Department of Medicine
University of Washington School of Medicine
Redmond, Washington

REVIEWERS

Mary C. Tobin, MD, Oak Park, Illinois
Jeffrey A. Wald, MD, Overland Park, Kansas
Dana V. Wallace, MD, Fort Lauderdale, Florida
Stephen Wasserman, MD, La Jolla, California

CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial
IIa Evidence from at least on controlled study without randomization
IIb Evidence from at least one other type of quasiexperimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

NR Not rated

PREFACE

Anaphylaxis is defined for the purposes of this document as a condition caused by an IgE-mediated reaction. Anaphylactoid reactions are defined as those reactions that produce the same clinical picture as anaphylaxis but are not IgE mediated. Where both IgE-mediated and non–IgE-mediated mechanisms are a possible cause, the term ''anaphylactic'' has been used to describe the reaction.

Anaphylactic reactions are often life-threatening and almost always unanticipated. Even when there are mild symptoms initially, the potential for progression to a severe and even irreversible outcome must be recognized. Any delay in the recognition of the initial signs and symptoms of anaphylaxis can result in a fatal outcome either because of airway obstruction or vascular collapse.

Most patients who have experienced anaphylaxis should be evaluated by a specialist in allergy-immunology. Such a consultation is appropriate because individuals trained in allergy-immunology possess particular training and skills to evaluate and appropriately treat individuals at risk of anaphylaxis.

The objective of this parameter, ''The diagnosis and management of anaphylaxis: an updated practice parameter,'' is to improve the care of patients by providing the practicing physician with an evidence-based approach to the diagnosis and management of anaphylactic reactions.

''The diagnosis and management of anaphylaxis: an updated practice parameter'' was developed by the Joint Task Force on Practice Parameters, which has published 11 practice parameters for the field of allergy-immunology (see list of publications). The 3 national allergy and immunology societies—the American College of Allergy, Asthma and Immunology (ACAAI); the American Academy of Allergy, Asthma and Immunology (AAAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI)—have given the Joint Task Force the responsibility for both creating new parameters and updating existing parameters. This parameter builds on ''The diagnosis and management of anaphylaxis,'' which was published in 1998 by the Joint Task Force on Practice Parameters. It was written and reviewed by specialists in the field of allergy and immunology and was exclusively funded by the 3 allergy and immunology organizations noted above.

A workgroup chaired by Phillip Lieberman, MD, prepared the initial draft. The Joint Task Force then reworked the initial draft into a working draft of the document. A comprehensive search of the medical literature was conducted with various search engines, including PubMed, using appropriate search terms. Published clinical studies were rated by category of evidence and used to establish the strength of the clinical recommendations (see ''Classification of rating and evidence'' above). The working draft of this updated parameter was reviewed by a large number of experts on anaphylaxis selected by the sponsoring organizations. This document represents an evidence-based and broadly accepted consensus viewpoint on the diagnosis and management of anaphylaxis.

''The diagnosis and management of anaphylaxis: an updated practice parameter'' contains annotated algorithms that present the major decision points for the initial evaluation and management of a patient with a history of a previous episode of anaphylaxis and for the acute management of anaphylaxis. These are followed by a list of summary statements that represent the key points to consider in the evaluation and management of anaphylaxis. These summary statements can also be found before each section in this document followed by the text that supports the summary statements, which are, in turn, followed by graded references that support the statements in the text. In addition to sections on the diagnosis and management of anaphylaxis, this updated parameter contains sections on anaphylaxis to foods, latex, seminal fluid, allergen immunotherapy, and medications, as well as exercise-induced anaphylaxis, idiopathic anaphylaxis, and anaphylaxis occurring during general anesthesia, both during the intraoperative and postoperative periods.

Among the objectives of this updated parameter are the development of an improved understanding of anaphylaxis among health care professionals, medical students, interns, residents, and fellows, as well as managed care executives and administrators. The parameter is intended to provide guidelines and support for the practicing physician and to improve the quality of care for patients who experience anaphylaxis. The Joint Task Force on Practice Parameters recognizes that there are different, although appropriate, approaches to the diagnosis and management of anaphylactic reactions that often require flexible recommendations. Therefore the diagnosis and management of anaphylactic reactions must be individualized on the basis of unique features in particular patients.

Throughout this document, we will rely on anaphylaxis to imply anaphylactic (IgE-mediated) and anaphylactoid (non–IgE-mediated) reactions.

The Joint Task Force on Practice Parameters wishes to thank the ACAAI, AAAAI, and JCAAI, who have supported the preparation of this updated parameter, and the large number of individuals who have so kindly dedicated their time and effort to the review of this document.

ALGORITHM FOR INITIAL EVALUATION AND MANAGEMENT OF A PATIENT WITH A HISTORY OF ANAPHYLAXIS (Fig 1)

Annotation 1: Is the history consistent with a previous episode of anaphylaxis?

All individuals who have had a known or suspected anaphylactic episode require a careful and complete review of their clinical history. This history might elicit manifestations, such as urticaria, angioedema, flushing, pruritus, upper airway obstruction, gastrointestinal symptoms, syncope, hypotension, lower airway obstruction, and/or dizziness.

Of primary importance is the nature of the symptoms characterizing the event. Essential questions to be asked are as follows:

1. Were there cutaneous manifestations, specifically pruritus, flush, urticaria, and angioedema?
2. Was there any sign of airway obstruction involving either the upper airway or the lower airway?
3. Were there gastrointestinal symptoms (ie, nausea, vomiting, or diarrhea)?
4. Were syncope or presyncopal symptoms present?

At this point, it should be noted that the absence of cutaneous symptoms puts the diagnosis in question because the majority of anaphylaxis includes cutaneous symptoms, but their absence would not necessarily rule out an anaphylactic or anaphylactoid event.

The history should concentrate on agents encountered before the reaction. Whenever appropriate, the information should be obtained from not only the patient but also family members or other witnesses. The complete sequence of events must be reviewed, with special attention paid to the cardiorespiratory symptoms. Medical records, including medication records, can often be useful in evaluating the history, physical findings, and treatment of the clinical event. In addition, the results of any previous laboratory studies (eg, serum tryptase levels) might be helpful in making the diagnosis of anaphylaxis or distinguishing it from other entities.

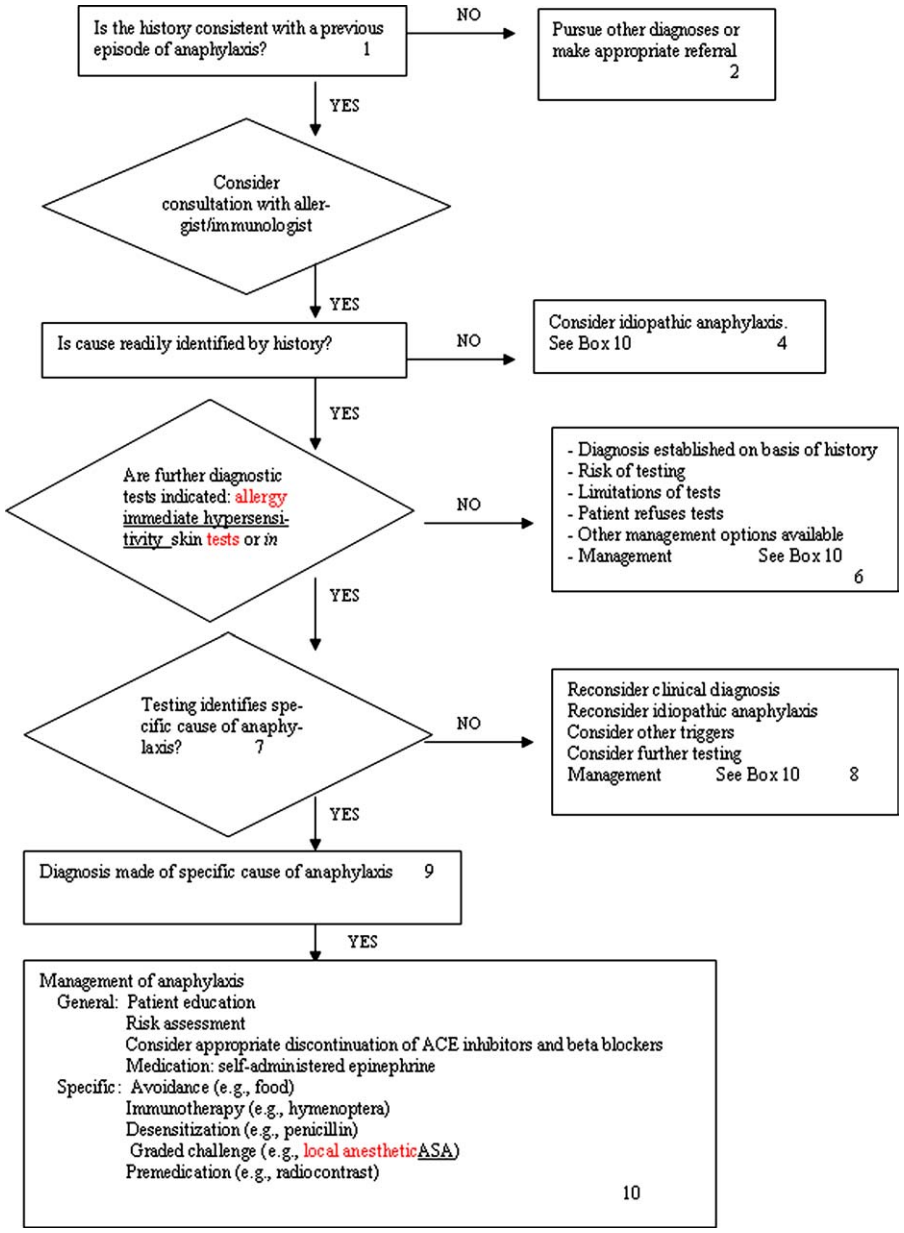


FIG 1. Algorithm for the initial evaluation and management of a patient with a history of an episode of anaphylaxis. *ACE,* Angiotensin-converting enzyme.

Annotation 1A: Consider consultation with an allergist-immunologist

Patients with anaphylaxis might be first seen with serious and life-threatening symptoms. Evaluation and diagnosis, as well as long-term management, can be complex. The allergist-immunologist has the training and expertise to obtain a detailed allergy history, coordinate laboratory and allergy testing, evaluate the benefits and risks of therapeutic options, and counsel the patient on avoidance measures. For these reasons, patients with a history of anaphylaxis should be considered for referral to an allergy-immunology specialist.

Annotation 2: Pursue other diagnoses or make appropriate referral

Other conditions that should be considered in the differential diagnosis include the following: (1) vasodepressor (vasovagal-neurocardiogenic) syncope; (2) syndromes that can be associated with flushing (eg, metastatic carcinoid); (3) postprandial syndromes (eg, scombroid poisoning); (4) systemic mastocytosis; (5) psychiatric disorders that can mimic anaphylaxis, such as panic attacks or vocal cord dysfunction syndrome; (6) angioedema (eg, hereditary angioedema); (7) other causes of shock (eg, cardiogenic); and (8) other cardiovascular or respiratory events.

Annotation 3: Is cause readily identified by history?

The history is the most important tool to establish the cause of anaphylaxis and takes precedence over diagnostic tests. A detailed history of all ingestants (both foods and drugs) several hours before the episode should be obtained. In addition, the labels for all packaged foods ingested by the patient in this period of time should be reviewed because a substance added to the food (eg, carmine) could be responsible. A history of any preceding bite or sting should be obtained. The patient's activities (eg, exercise, sexual activity, or both) preceding the event should be reviewed. Patient diaries might be a useful adjunct in confirming and identifying the cause of anaphylaxis.

Annotation 4: Consider idiopathic anaphylaxis

Idiopathic anaphylaxis is a diagnosis of exclusion that should be made only after other causes of anaphylaxis and other differential diagnoses have been considered.

Annotation 5: Are further diagnostic tests indicated: immediate hypersensitivity or *in vitro* tests, challenge tests?

Immediate hypersensitivity tests or *in vitro* specific IgE tests and/or challenge tests might be appropriate to help define the cause of the anaphylactic episode. However, the history might be so specific that none of the above tests are necessary.

Annotation 6: Diagnosis established on basis of history, risk of testing, limitation of tests, patient refuses test, other management options available, management

There might be circumstances in which allergy skin tests, *in vitro* specific IgE tests, and/or challenge tests might not be warranted. In general, this might apply when the clinician (with the consent of the patient) decides to proceed with management on the basis of the history and physical examination.

For example, the clinical history of anaphylaxis to a specific agent might be so strong that testing is unnecessary (or dangerous). Conversely, the medical history of anaphylaxis might be sufficiently mild or weak that management can proceed in the absence of testing. If avoidance can be easily and safely accomplished, testing might not be necessary.

Furthermore, testing or challenge with reagents to a suspected allergen might not be available, or the accuracy of the test might be in question. In addition, for patients with a history of anaphylaxis, challenge tests (and, to a lesser extent, skin tests) might be hazardous.

Annotation 7: Testing identifies specific cause of anaphylaxis

Skin tests or *in vitro* tests that determine the presence of specific IgE antibodies can identify specific causes of anaphylaxis. Causes of anaphylaxis that can be defined in this way include foods, medications (eg, penicillin and insulin), and stinging insects. For the majority of medications, standardized testing either by *in vivo* or *in vitro* means is not available. Such tests are only valid when the reaction is due to a true anaphylactic event (IgE-mediated reaction) and not as a result of an anaphylactoid (non–IgE-mediated) reaction.

In general, skin testing is more sensitive than *in vitro* testing and is the diagnostic procedure of choice for evaluation of most potential causes of anaphylaxis (eg, penicillin, insect stings, and foods). It is essential that the correct technique for skin testing be used to obtain meaningful data regarding causative agents of anaphylaxis. When possible, standardized extracts should be used (occasionally fresh food extracts will be superior to available standardized extracts). If the skin testing extract has not been standardized (eg, latex, protamine, or antibiotics other than penicillin), the predictive value is uncertain. If skin testing is performed, it should be done under the supervision of a physician who is experienced in the procedure in a setting with appropriate rescue equipment and medication.

The accuracy of *in vitro* testing depends on the reliability of the *in vitro* method, the ability to interpret the results, and the availability of reliable testing material. The clinical significance of skin test or *in vitro* test results depends on the ability to correlate such results with the patient's history.

If tests for specific IgE antibodies (ie, skin tests, *in vitro* tests, or both) do not provide conclusive evidence of the cause of anaphylaxis, challenge with the suspected agent can be considered. Challenge procedures might also be appropriate in patients with anaphylactoid reactions (eg, reactions to aspirin or other nonsteroidal anti-inflammatory drugs). Challenges with suspected agents must be done carefully by individuals knowledgeable in the challenge procedure and with expertise in managing reactions to the challenge agent if they should occur.

Annotation 8: Reconsider clinical diagnosis, reconsider idiopathic anaphylaxis, consider other triggers, consider further testing, management

At this stage in the patient's evaluation, it is particularly important to consider other trigger factors and diagnoses. The medical history and laboratory test results should be reviewed. Further testing for specific IgE antibodies should be considered. Laboratory studies that might be helpful include serum tryptase measurement, as well as urinary 5-hydroxyindoleacetic acid, methylhistamine, and catecholamine measurement. Idiopathic anaphylaxis is a diagnosis of exclusion (see ''Idiopathic anaphylaxis'').

Management of anaphylaxis episodes should follow annotation 10 (see algorithm).

Annotation 9: Diagnosis made of specific cause of anaphylaxis

The diagnosis of a specific cause of anaphylaxis might be supported by the results of skin tests, *in vitro* IgE tests, and/or challenge tests (particularly double-blind, placebo-controlled challenge tests).

Annotation 10: Management of anaphylaxis

When anaphylaxis has occurred because of exposure to a specific agent (eg, food, medication, or insect sting), patients should be educated about agents or exposures that would place them at risk for future reactions and be counseled on avoidance measures that might be used to reduce risk for such exposures. Patients who have had anaphylactic reactions to food should be instructed on how to read food ingredient labels to identify foods that they should avoid. Patients with anaphylaxis to medications should be informed about all cross-reacting medications that should be avoided. Should there be a future essential indication for use of incriminated medications, it might be helpful to educate patients about applicable management options (eg, medication pretreatment and use of low-osmolarity agents in patients with a history of reactions to radiographic contrast media or desensitization for drugs, such as antibiotics). Patients who have had anaphylactic reactions to insect stings should be advised about avoidance measures to reduce the risk of insect stings are candidates for insect venom immunotherapy (see ''Stinging insect hypersensitivity: a practice parameter update''). Patients who have had anaphylaxis should carry self-injectable epinephrine for use if anaphylaxis develops. There might be exceptions to this (eg, anaphylaxis to penicillin). Patients should also carry identification indicating that they are prone to anaphylaxis and indicating the responsible agent. Patients taking β-blockers are at increased risk during anaphylaxis.

ALGORITHM FOR THE TREATMENT OF ACUTE ANAPHYLAXIS (Fig 2)

Annotation 1. Anaphylaxis preparedness

It is important to stress that management recommendations are subject to physician discretion and that variations in sequence and performance rely on physician judgment. Additionally, a determination of when a patient should be transferred to an emergency facility depends on the skill, experience, and clinical decision making of the individual physician. Preparedness, prompt recognition, and appropriate and aggressive treatment are integral to parts of successful management of anaphylaxis. A treatment log will assist in accurately recording progress (Fig 3).

Recommendations depend on practice resources and the proximity to other emergency assistance. Stocking and maintaining anaphylaxis supplies with regular written documentation of contents and expiration dates and ready availability of injectable epinephrine, intravenous fluids and needles, oxygen and mask cannula, airway adjuncts, and stethoscope and sphygmomanometer are bare essentials. (An example of a supply checklist is included in ''Management of anaphylaxis'' [Fig 4]. Not all items need to be present in each office.)

Regular anaphylaxis practice drills, the contents of which are left to the discretion and qualifications of the individual physician, are strongly recommended. Essential ingredients are identification of a person who will be responsible for calling emergency medical services and the person who will document treatment and time each is rendered. The emergency kit should be up to date and complete. Everyone who will be directly involved in patient care should, for example, be able to easily locate necessary supplies and rapidly assemble fluids for intravenous administration.

Annotation 2. Patient presents with possible-probable acute anaphylaxis

Anaphylaxis is an acute life-threatening reaction, usually but not always mediated by an immunologic mechanism (anaphylactoid reactions are IgE independent), that results from the sudden systemic release of mast cells and basophil mediators. It has varied clinical presentations, but respiratory compromise and cardiovascular collapse cause the most concern because they are the most frequent causes of fatalities. Urticaria and angioedema are the most common manifestations of anaphylaxis but might be delayed or absent in rapidly progressive anaphylaxis. The more rapidly anaphylaxis occurs after exposure to an offending stimulus, the more likely the reaction is to be severe and potentially life-threatening.

Anaphylaxis often produces signs and symptoms within minutes of exposure to an offending stimulus (see comments in text), but some reactions might develop later (eg, >30 minutes after exposure). Late-phase or biphasic reactions, which occur 8 to 12 hours after the initial attack, have also been reported. Protracted and severe anaphylaxis might last up to 32 hours, despite aggressive treatment.

Increased vascular permeability, a characteristic feature of anaphylaxis, allows transfer of as much as 50% of the intravascular fluid into the extravascular space within 10 minutes. As a result, hemodynamic collapse might occur rapidly with little or no cutaneous or respiratory manifestations.

Annotation 3. Initial assessment supports potential anaphylaxis

Initial assessment should determine whether history and physical findings are compatible with anaphylaxis. The setting of the episode and the history might suggest or reveal the source of the reaction. Evaluation should include level of consciousness (impairment might reflect hypoxia), upper and lower airways (dysphonia, stridor, cough, wheezing, or shortness of breath), cardiovascular system (hypotension with or without syncope and/or

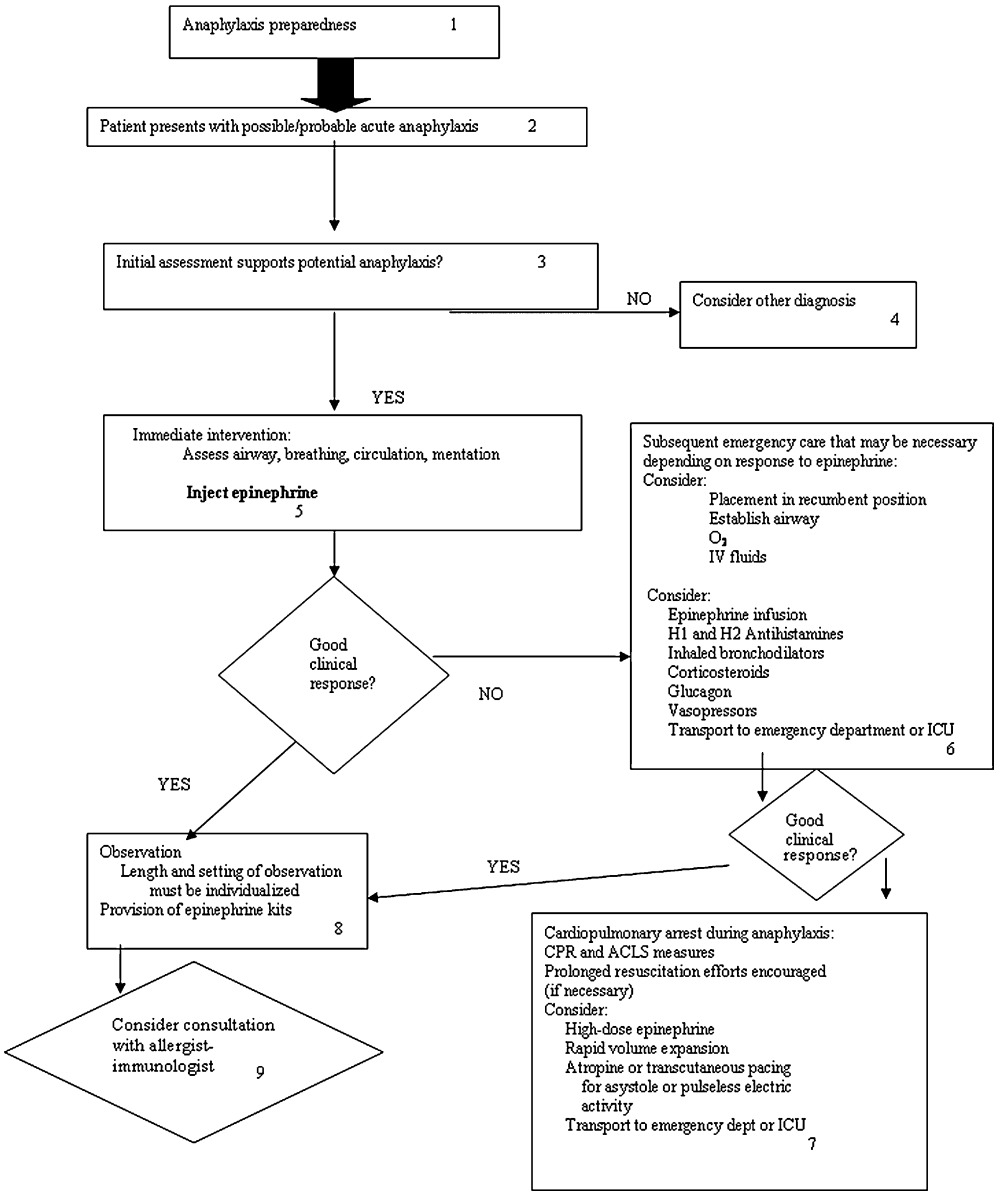


FIG 2. Algorithm for the treatment of acute anaphylaxis. *ICU,* Intensive care unit; *CPR,* cardiopulmonary resuscitation; *ACLS,* advanced cardiac life support.

cardiac arrhythmias), the skin (diffuse or localized erythema, pruritus, urticaria, and/or angioedema), and the gastrointestinal system (nausea, vomiting, or diarrhea). In addition, some patients might have symptoms of lightheadedness, headache, uterine cramps, feeling of impending doom, and unconsciousness.

The vasodepressor (vasovagal) reaction probably is the condition most commonly confused with anaphylactic and anaphylactoid reactions. In vasodepressor reactions, however, urticaria is absent, the heart rate is typically bradycardic, bronchospasm or other breathing difficulty is generally absent, the blood pressure is usually normal or increased, and the skin is typically cool and pale. Tachycardia is the rule in anaphylaxis, but it might be absent in patients with conduction defects, with increased vagal tone caused by a cardioinhibitory (Bezold-Jarisch) reflex, or who take sympatholytic medications.

Annotation 4. Consider other diagnosis

Other diagnoses that might present with signs and/or symptoms characteristic of anaphylaxis should be excluded. Like anaphylaxis, several conditions might cause abrupt and dramatic patient collapse. Among conditions to consider are vasodepressor (vasovagal) reactions, acute anxiety (eg, panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, systemic mast cell disorders, foreign-body aspiration, acute poi-

Name_____ Date_____
Date of Birth_____ Prescribing Physician_____

Prior systemic rxn:_____ Hx of asthma?_____
Date/time of rxn:_____

History of the systemic reaction (SR):

Immediate measures:
__Assess airway, breathing, circulation, and orientation
__Injectable Epinephrine
__Activate EMS (call 911 or local rescue squad) Y/N Time called:_____AM/PM
__Management algorithm reviewed (as needed)

Signs & Symptoms (*Circle pertinent findings*):

Respiratory:	**Skin:**	**Eye/Nasal:**	**Vascular:**	**Other:**
Dyspnea, chest tightness	Urticaria	Runny nose	Hypotension	Difficulty swallowing
Wheezing	Angioedema	Red eyes	Chest discomfort	Abdominal pain, nausea, emesis, diarrhea
Cough	Generalized itch	Congestion	Dizziness, syncope	Diaphoresis
Stridor	Flushing	Sneezing	Headache	Apprehension

Resp. rate/ Time	Pulse/ PEFR	O_2 %Sat	BP	Intervention, Meds, Exam, Comments

Time (AM/PM)/ Condition upon release:_____
Patient instructions:_____
Follow-up call to patient: Time_____ Comments:_____
Clinical impression: **True SR** **Questionable SR** **No SR**

Signatures_____ RN _____MD/DO

Modified with permission from: Kemp SF. "Anaphylaxis Committee Proposals to Improve Safety of Skin Testing and Immunotherapy Administration". *Allergen Immunotherapy: Increasing Effectiveness and Safety with Specific Measures to Improve Standardized Materials, Methods, Forms and Procedures*. Symposium, 58th Annual Meeting of the American Academy of Allergy, Asthma and Immunology, New York, New York, March 2, 2002. Original modified with permission from form used by Linda Cox, MD, Ft. Lauderdale, Florida.

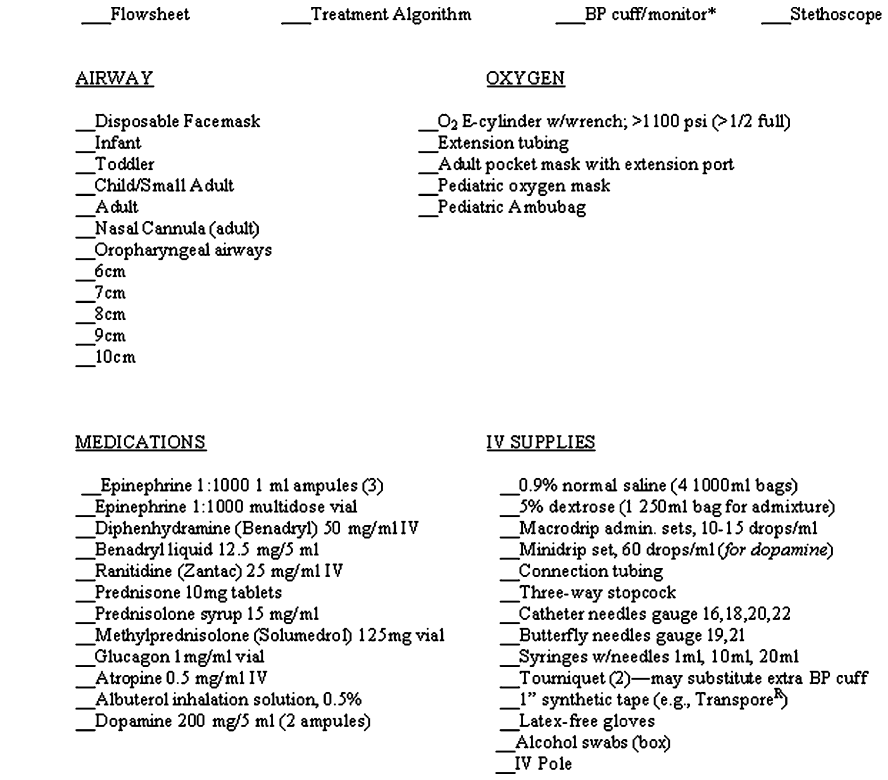
FIG 3. Anaphylaxis treatment record.

soning, hypoglycemia, and seizure disorder. Specific signs and symptoms of anaphylaxis might present singly in other disorders. Examples are urticaria-angioedema, hereditary angioedema, and asthma.

Annotation 5. Immediate intervention

The clinician should remember that anaphylaxis occurs as part of a continuum. Symptoms not immediately life-threatening might progress rapidly unless treated promptly. Treatment recommendations are subject to physician discretion, and variations in sequence and performance rely on physician judgment. Additionally, a determination of when a patient should be transferred to an emergency or intensive care facility depends on available resources and the skill, experience, and clinical decision making of the individual physician.

1. Assess airway, breathing, circulation, and level of consciousness (altered mentation might suggest the presence of hypoxia).
2. Administer epinephrine. Aqueous epinephrine 1:1000 dilution (1 mg/mL), 0.2 to 0.5 mL (0.01 mg/kg in children, maximum 0.3-mg dosage) intramuscularly or subcutaneously every 5 minutes, as necessary, should be used to control symptoms and increase blood pressure. Consider dose-response effects. *Note:* If the clinician deems it appropriate, the 5-minute interval between injections can be liberalized to permit more frequent injections. Intramuscular epinephrine injections into the thigh have been reported to provide more rapid absorption and higher plasma epinephrine levels in both children and adults than intramuscular or subcutaneous injections administered in the arm. However, similar studies comparing intramuscular injections with subcutaneous injections in the thigh have not yet been done. Moreover, these studies were not performed in patients experiencing anaphylaxis. For this reason, the generalizability of these findings to the clinical setting of anaphylaxis has not been established. Although intuitively more rapid absorption and higher epinephrine levels would seem desirable, the clinical significance of this finding is not known. No data support the use of epinephrine in anaphylaxis through a nonparenteral route. However, alternative routes of administration have been anecdotally



___Flowsheet ___Treatment Algorithm ___BP cuff/monitor* ___Stethoscope

AIRWAY

__Disposable Facemask
__Infant
__Toddler
__Child/Small Adult
__Adult
__Nasal Cannula (adult)
__Oropharyngeal airways
__6cm
__7cm
__8cm
__9cm
__10cm

OXYGEN

__O_2 E-cylinder w/wrench; >1100 psi (>1/2 full)
__Extension tubing
__Adult pocket mask with extension port
__Pediatric oxygen mask
__Pediatric Ambubag

MEDICATIONS

__Epinephrine 1:1000 1 ml ampules (3)
__Epinephrine 1:1000 multidose vial
__Diphenhydramine (Benadryl) 50 mg/ml IV
__Benadryl liquid 12.5 mg/5 ml
__Ranitidine (Zantac) 25 mg/ml IV
__Prednisone 10mg tablets
__Prednisolone syrup 15 mg/ml
__Methylprednisolone (Solumedrol) 125mg vial
__Glucagon 1mg/ml vial
__Atropine 0.5 mg/ml IV
__Albuterol inhalation solution, 0.5%
__Dopamine 200 mg/5 ml (2 ampules)

IV SUPPLIES

__0.9% normal saline (4 1000ml bags)
__5% dextrose (1 250ml bag for admixture)
__Macrodrip admin. sets, 10-15 drops/ml
__Minidrip set, 60 drops/ml (*for dopamine*)
__Connection tubing
__Three-way stopcock
__Catheter needles gauge 16,18,20,22
__Butterfly needles gauge 19,21
__Syringes w/needles 1ml, 10ml, 20ml
__Tourniquet (2)—may substitute extra BP cuff
__1" synthetic tape (e.g., Transpore®)
__Latex-free gloves
__Alcohol swabs (box)
__IV Pole

*Sphygmomanometer/electronic BP monitoring device should be calibrated annually. A minimum of 3 cuff sizes should be available (child, adult, obese/large adult).

Replace supplies within one month of expiration date. Check supplies monthly and re-stock after use. Sphygmomanometer and oxygen tank connections should be checked weekly for air leak or malfunction.

Note: Not all items need to be present in each treatment setting.

Initials: _____
Date: _____

Modified with permission from: Kemp SF. "Anaphylaxis Committee Proposals to Improve Safety of Skin Testing and Immunotherapy Administration". *Allergen Immunotherapy: Increasing Effectiveness and Safety with Specific Measures to Improve Standardized Materials, Methods, Forms and Procedures*. Symposium, 58th Annual Meeting of the American Academy of Allergy, Asthma and Immunology, New York, New York, March 2, 2002.

FIG 4. Suggested anaphylaxis supply check sheet

successful. These include, for example, inhaled epinephrine in the presence of laryngeal edema or sublingual administration if an intravenous route cannot be obtained. Endotracheally administered dosages have also been proposed for use when intravenous access is not available in intubated patients experiencing cardiac arrest.

Annotation 6. Subsequent emergency care that might be necessary depending on response to epinephrine

1. Place patient in the recumbent position and elevate the lower extremities, as tolerated symptomatically. This slows progression of hemodynamic compromise, if present, by preventing orthostatic hypotension and helping to shunt effective circulation from the periphery to the head and to the heart and kidneys.
2. Establish and maintain airway. Ventilatory assistance through a 1-way valve facemask with an oxygen inlet port (eg, Pocket-Mask [Laerdal®, Preparedness Industries, Ukiah, Calif] or similar device) might be necessary. Ambubags of less than 700 mL are discouraged in adults in the absence of an endotracheal tube because ventilated volume will not overcome 150 to 200 mL of anatomic dead space to provide effective tidal volume. (Ambubags can be used in children, provided the reservoir volume of the device is sufficient.) Endotracheal intubation or cricothyroidotomy might be considered where appropriate and provided that clinicians are adequately trained and proficient in this procedure.
3. Administer oxygen. Oxygen should be administered to patients with anaphylaxis who have prolonged reactions, have pre-existing hypoxemia or myocardial dysfunction, receive inhaled β-agonists as part of

therapy for anaphylaxis, or require multiple doses of epinephrine. Continuous pulse oximetry and/or arterial blood gas determination (where available) should guide oxygen therapy where hypoxemia is a concern.

4. Consider a normal saline intravenous line for fluid replacement and venous access. Lactated Ringer's solution might potentially contribute to metabolic acidosis, and dextrose is rapidly extravasated from the intravascular circulation to the interstitial tissues. Increased vascular permeability in anaphylaxis might permit transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes. Crystalloid volumes (eg, saline) of up to 7 L might be necessary. One to 2 L of normal saline should be administered to adults at a rate of 5 to 10 mL/kg in the first 5 minutes. Patients with congestive heart failure or chronic renal disease should be observed cautiously to prevent volume overload. Children should receive up to 30 mL/kg in the first hour. Adults receiving colloid solution should receive 500 mL rapidly, followed by slow infusion. Aqueous epinephrine 1:1000, 0.1 to 0.3 mL in 10 mL of normal saline, can be administered intravenously over several minutes and repeated as necessary in cases of anaphylaxis not responding to epinephrine injections and volume resuscitation. Alternatively, an epinephrine infusion can be prepared by adding 1 mg (1 mL) of a 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4.0 μg/mL. This solution is infused at a rate of 1 to 4 μg/min (15 to 60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10.0 μg/min. If an infusion pump is available, an alternative 1:100,000 solution of epinephrine (1 mg [1 mL] in 100 mL of saline) can be prepared and administered intravenously at an initial rate of 30 to 100 mL/h (5-15 μg/min), titrated up or down depending on clinical response or epinephrine side effects (toxicity). A dosage of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the ''rule of 6'' is as follows: 0.6× body weight (in kilograms) = the number of milligrams diluted to a total of 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min. *Note:* Because of the risk for potentially lethal arrhythmias, epinephrine should be administered intravenously only during cardiac arrest or to profoundly hypotensive patients who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations in which hemodynamic monitoring is available (eg, emergency department or intensive care facility), continuous hemodynamic monitoring is essential. However, use of intravenous epinephrine should not be precluded in a scenario in which such monitoring is unavailable if the clinician deems administration is essential after failure of several epinephrine injections. If intravenous epinephrine is considered essential under these special circumstances, monitoring by available means (eg, every-minute blood pressure and pulse measurements and electrocardiographic monitoring, if available) should be conducted.
5. Consider diphenhydramine, 1 to 2 mg/kg or 25 to 50 mg per dose (parenterally). *Note:* H_1 antihistamines are considered second-line therapy to epinephrine and should never be administered alone in the treatment of anaphylaxis.
6. Consider ranitidine, 50 mg in adults and 12.5 to 50 mg (1 mg/kg) in children, which might be diluted in 5% dextrose to a total volume of 20 mL and injected intravenously over 5 minutes. Cimetidine (4 mg/kg) can be administered intravenously to adults, but no pediatric dosage in anaphylaxis has been established. *Note:* In the management of anaphylaxis, a combination of diphenhydramine and ranitidine is superior to diphenhydramine alone. However, these agents have a much slower onset of action than epinephrine and should never be used alone in the treatment of anaphylaxis. Both alone and in combination, these agents are second-line therapy to epinephrine.
7. Bronchospasm resistant to adequate doses of epinephrine: consider inhaled β-agonist (eg, nebulized albuterol, 2.5 to 5 mg in 3 mL of saline and repeat as necessary).
8. Hypotension refractory to volume replacement and epinephrine injections: consider vasopressor infusion. Continuous hemodynamic monitoring is essential. For example, dopamine (400 mg in 500 mL of 5% dextrose) can be infused at 2 to 20 μg/kg/min and titrated to maintain systolic blood pressure of greater than 90 mm Hg.
9. Consider glucagon infusion when concomitant β-adrenergic blocking agent complicates treatment. Glucagon dosage is 1 to 5 mg (20-30 μg/kg [maximum dose, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion (5 to 15 μg/min) titrated to clinical response.
10. Consider systemic glucocorticosteroids for patients with a history of idiopathic anaphylaxis or asthma and patients who experience severe or prolonged anaphylaxis. Glucocorticosteroids usually are not helpful acutely but potentially might prevent recurrent or protracted anaphylaxis. If given, intravenous glucocorticosteroids should be administered every 6 hours at a dosage equivalent to 1.0 to 2.0 mg/kg/d. Oral administration of glucocorticosteroids (eg, prednisone, 0.5 mg/kg) might be sufficient for less critical anaphylactic episodes.
11. Consider transportation to emergency department or intensive care facility.

Annotation 7. Cardiopulmonary arrest during anaphylaxis

1. Cardiopulmonary resuscitation and advanced cardiac life support measures.
2. High-dose epinephrine administered intravenously (ie, rapid progression to high dose). A common sequence

is 1 to 3 mg (1:10,000 dilution) slowly administered intravenously over 3 minutes, 3 to 5 mg administered intravenously over 3 minutes, and then a 4 to 10 μg/min infusion. For children, the recommended initial resuscitation dosage is 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution up to 10 μg/min rate of infusion) repeated every 3 to 5 minutes for ongoing arrest. Higher subsequent dosages (0.1-0.2 mg/kg; 0.1 mL/kg of a 1:1,000 solution) might be considered for unresponsive asystole or pulseless electrical activity.
3. Rapid volume expansion.
4. Atropine and transcutaneous pacing if asystole and/or pulseless electrical activity are present.
5. Prolonged resuscitation is encouraged, if necessary, because efforts are more likely to be successful in anaphylaxis.
6. Transport to emergency department or intensive care facility, as setting dictates.

Annotation 8. Observation and subsequent follow-up

Observation periods must be individualized because there are no reliable predictors of biphasic or protracted anaphylaxis on the basis of initial clinical presentation. Follow-up accordingly must be individualized and based on such factors as clinical scenario and distance from the patient's home to the closest emergency facility. After resolution of the acute episode, patients should be provided with an epinephrine syringe and receive proper instruction for self-administration in case of a subsequent episode. In circumstances in which an allergist-immunologist is not already involved, it is strongly recommended that individuals who have experienced acute anaphylaxis should receive consultation from an allergist-immunologist regarding diagnosis, prevention, and treatment.

Annotation 9. Consider consultation with an allergist-immunologist

After acute anaphylaxis, patients should be assessed for future risk for anaphylaxis. The allergist-immunologist can obtain a detailed history, coordinate allergy diagnostic testing, evaluate the risks and benefits of therapeutic options, train and retrain in self-administration of epinephrine, and provide counseling on avoidance measures (the most effective treatment for most causes of anaphylaxis).

Consultation with an allergist-immunologist is recommended when:

1. the diagnosis is doubtful or incomplete;
2. the symptoms are recurrent or difficult to control;
3. help is needed in evaluation and management of medication use or side effects;
4. help is needed in medical management or adherence to treatment;
5. help is needed in the diagnosis or management of IgE-mediated reactions or identification of allergic triggers;
6. the patient is a candidate for desensitization (eg, penicillin) or immunotherapy (eg, venom-specific immunotherapy);
7. the patient requires daily medications for prevention;
8. the patient requires intensive education regarding avoidance or management;
9. help is needed with new or investigative therapy;
10. treatment goals have not been met;
11. anaphylaxis is complicated by one or more comorbid conditions or concomitant medications; or
12. the patient has requested a subspecialty consultation.

SUMMARY STATEMENTS

Evaluation and management of the patient with a history of episodes of anaphylaxis

1. The history is the most important tool to determine whether a patient has had anaphylaxis and the cause of the episode. **C**
2. A thorough differential diagnosis should be considered, and other conditions should be ruled out. **C**
3. Laboratory tests can be helpful to confirm a diagnosis of anaphylaxis or rule out other causes. Proper timing of studies (eg, serum tryptase) is essential. **B**
4. In the management of a patient with a previous episode, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. **C**
5. The patient should be instructed to wear and/or carry identification denoting his or her condition (eg, Medic Alert jewelry). **C**

Management of anaphylaxis

6. Medical facilities should have an established protocol to deal with anaphylaxis and the appropriate equipment to treat the episode. In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand. **B**
7. Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils. **B**
8. Anaphylactic (IgE-dependent) and anaphylactoid (IgE-independent) reactions differ mechanistically, but the clinical presentations are identical. **C**
9. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. **C**
10. Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. **C**
11. Any health care facility should have a plan of action for anaphylaxis should it occur. Physicians and office staff should maintain clinical proficiency in anaphylaxis management. **D**
12. Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Epinephrine is the drug of choice, and the appropriate

dose should be administered promptly at the onset of apparent anaphylaxis. **A/D**

13. Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital is essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting. **B**

Anaphylaxis to foods

14. Severe food reactions have been reported to involve the gastrointestinal, cutaneous, respiratory, and cardiovascular systems. **D**
15. The greatest number of anaphylactic episodes in children has involved peanuts, tree nuts (ie, walnuts, pecans, and others), fish, shellfish, milk, and eggs **(C)**. The greatest number of anaphylactic episodes in adults is due to shellfish **(C)**. Clinical cross-reactivity with other foods in the same group is unpredictable **(B)**. Additives can also cause anaphylaxis **(C)**.
16. Anaphylactic reactions to foods almost always occur immediately. Symptoms might then subside, only to recur several hours later. **A**
17. The most useful diagnostic tests include skin tests and food challenges. *In vitro* testing with foods might be appropriate as an alternative screening procedure. **C**
18. Double- or single-blind placebo-controlled food challenges can be done in patients with suspected food allergy in a medical facility by personnel experienced in performing the procedure and prepared to treat anaphylaxis. **B**
19. Patient education should include discussion about avoidance and management of accidental ingestion. **C**
20. Schools might present a special hazard for the student with food allergy. Epinephrine should be available for use by the individuals in the school trained to respond to such a medical emergency. **C**

Latex-induced anaphylaxis

21. Latex (rubber) hypersensitivity is a significant medical problem, and 3 groups are at higher risk of reaction: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex. **B**
22. Skin prick tests with latex extracts should be considered for patients who are members of high-risk groups or who have a clinical history of possible latex allergy to identify IgE-mediated sensitivity. Although a standardized, commercial skin test reagent for latex is not available in the United States, many allergy centers have prepared latex extracts from gloves to be used for clinical testing. It should be noted, however, that such extracts prepared from gloves demonstrate tremendous variability in content of latex antigen. *In vitro* assays for IgE to latex might also be useful, although these tests are generally less sensitive than skin tests. **C**
23. Patients with spina bifida (regardless of a history of latex allergy) and other patients with a positive history of latex allergy ideally should have all medical-surgical-dental procedures performed in a latex-safe environment and as the first case of the day. **D**
24. A latex-safe environment is an environment in which no latex gloves are used in the room or surgical suite and no latex accessories (catheters, adhesives, tourniquets, and anesthesia equipment) come into contact with the patient. **D**
25. In health care settings general use of latex gloves with negligible allergen content, powder-free latex gloves, and nonlatex gloves and medical articles should be considered in an effort to minimize exposure to latex allergen. Such a combined approach might minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals. **C**

Anaphylaxis during general anesthesia, the intraoperative period, and the postoperative period

26. The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4000 to 1 in 25,000. Anaphylaxis during anesthesia can present as cardiovascular collapse, airway obstruction, flushing, and/or edema of the skin. **C**
27. It might be difficult to differentiate between immune and nonimmune mast cell–mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia. **B**
28. Thiopental allergy has been documented by using skin tests. **B**
29. Neuromuscular blocking agents, such as succinylcholine, can cause nonimmunologic histamine release, but there have been reports of IgE-mediated mechanisms in some cases. **B**
30. Reactions to opioid analgesics are usually caused by direct mast cell–mediator release rather than IgE-dependent mechanisms. **B**
31. Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic generalized reactions. **B**
32. Protamine can also cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms. **B**
33. Latex is a potent allergen, and IgE-mediated reactions to latex during anesthesia have been clearly documented. Patients with multiple surgical procedures (eg, patients with spina bifida) and health care workers are at greater risk of latex sensitization. Precautions for latex-sensitive patients include avoiding the use of latex gloves and latex blood pressure cuffs, as well as latex intravenous tubing ports and rubber stoppers from medication vials. **B**
34. Blood transfusions can elicit a variety of systemic reactions, some of which might be IgE mediated or mediated through other immunologic mechanisms. **B**

35. Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no IgE mechanism has yet been documented. **C**
36. The evaluation of IgE-mediated reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents. **B**
37. The management of anaphylactic or anaphylactoid reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations. **B**

Seminal fluid-induced anaphylaxis

38. Anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization by proteins of varying molecular weights. **B**
39. Localized seminal plasma hypersensitivity has been well described and is likely IgE mediated on the basis of successful response to rapid seminal plasma desensitization. **C**
40. History of atopic disease is the most consistent risk factor. However, anecdotal case reports have been associated with gynecologic surgery, injection of anti-RH immunoglobulin, and the postpartum state. **C**
41. The diagnosis is confirmed by means of skin and/or *in vitro* tests for serum-specific IgE by using proper reagents obtained from fractionation of seminal fluid components. **C**
42. Prevention of reactions to seminal fluid can be accomplished by barrier use of condoms. **C**
43. Immunotherapy to properly fractionated seminal fluid proteins has been universally successful in preventing anaphylaxis to seminal fluid, provided the sensitizing seminal fluid fractions are used as immunogens. Successful intravaginal graded challenge with unfractionated seminal fluid has been reported in a few cases, but the duration of protection is unknown. **C**
44. Localized and/or systemic seminal plasma hypersensitivity is not associated with infertility. **D**

Exercise-induced anaphylaxis

45. Exercise-induced anaphylaxis is a form of physical allergy. Premonitory symptoms can include diffuse warmth, itching, and erythema. Urticaria generally ensues, with progression to confluence and often angioedema. Episodes can progress to include gastrointestinal symptoms, laryngeal edema, and/or vascular collapse. **B**
46. Factors that have been associated with exercise-induced anaphylaxis include medications (eg, aspirin and other nonsteroidal anti-inflammatory drugs) or food ingestion before and after exercise. **C**
47. Patients with exercise-induced anaphylaxis might have a higher incidence of personal and/or family history of atopy. **C**
48. Medications used prophylactically are not useful in preventing exercise-induced anaphylaxis. **C**
49. If exercise-induced anaphylactic episodes have been associated with the ingestion of food, exercise should be avoided in the immediate postprandial period. **C**
50. Patients with exercise-induced anaphylaxis should carry epinephrine and should wear and/or carry Medic Alert identification denoting their condition. They should have a companion with them when exercising. This companion should be versed in the use of an EpiPen. **D**

Idiopathic anaphylaxis

51. The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. **C**
52. Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. **C**
53. There might be a need for specific laboratory studies to exclude systemic disorders, such as systemic mastocytosis. This might include a serum tryptase level when the patient is asymptomatic, a ratio of β-tryptase to total tryptase during an event, and selective allergy skin testing. **C**

Anaphylaxis and allergen immunotherapy vaccines

54. There is a small risk of near-fatal and fatal anaphylactic reactions to allergen immunotherapy injections. **C**
55. Patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to allergen immunotherapy injections **(C)**. Patients taking β- adrenergic blocking agents are at higher risk for serious systemic reactions to allergen immunotherapy injections **(B)**.
56. Allergen immunotherapy vaccines should be administered only by health care professionals trained in the recognition and treatment of anaphylaxis, only in health care facilities with the proper equipment for the treatment of anaphylaxis, and in clinics with policies and procedures that minimize the risk of anaphylaxis. **D**

Anaphylaxis to drugs

57. Low-molecular-weight medications induce an IgE-mediated reaction only after combining with a carrier protein to produce a complete multivalent antigen. **B**
58. Penicillin is the most common cause of drug-induced anaphylaxis. **C**
59. Penicillin spontaneously degrades to major and minor antigenic determinants, and skin testing with reagents on the basis of these determinants yields negative results in about 90% of patients with a history of penicillin allergy. **B**
60. The negative predictive value of penicillin skin testing (for immediate-type reactions) is between 97% and 99% (depending on the reagents used), and the positive predictive value is at least 50%. **B**

61. The extent of allergic cross-reactivity between penicillin and cephalosporins is unknown but appears to be low. Four percent of patients proved to have penicillin allergy by means of penicillin skin testing react to cephalosporin challenges. **C**
62. Patients with a history of penicillin allergy who have negative penicillin skin test responses might safely receive cephalosporins. **B**
63. Patients with a history of penicillin allergy who have positive penicillin skin test responses might (1) receive an alternate (non–β-lactam) antibiotic, (2) receive a cephalosporin through graded challenge, or (3) receive a cephalosporin through rapid desensitization. **F**
64. Aztreonam does not cross-react with other β-lactams, except ceftazidime, with which it shares a common R-group side chain. **B**
65. Carbapenems should be considered cross-reactive with penicillin. **C**
66. Diagnosis of IgE-mediated reactions to non–β-lactam antibiotics is limited by a lack of knowledge of the relevant allergenic determinants and/or metabolites. **C**
67. Aspirin and nonsteroidal anti-inflammatory drugs are the second most common cause of drug-induced anaphylaxis. **C**
68. Anaphylactic reactions to aspirin and nonsteroidal anti-inflammatory drugs appear to be medication specific and do not cross-react with structurally unrelated aspirin or other nonsteroidal anti-inflammatory drugs. **D**

Prevention of anaphylaxis

69. Major risk factors related to anaphylaxis include, but are not limited to, prior history of such reactions, concomitant β-adrenergic blocker therapy, exposure, or atopic background. Atopic background might be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to medications.
70. Avoidance measures are successful if future exposure to drugs, foods, additives, or occupational allergens can be prevented. Avoidance of stinging and biting insects is also possible in many cases. Prevention of systemic reactions during allergen immunotherapy is dependent on the specific circumstances involved.
71. Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, access to medical care, and the patients' level of personal anxiety.
72. Pharmacologic prophylaxis should be used to prevent recurrent anaphylactoid reactions to radiographic contrast material, fluorescein, as well as to prevent idiopathic anaphylaxis. Prophylaxis with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions.

TABLE I. Frequency of occurrence of signs and symptoms of anaphylaxis*†

Signs and symptoms	
Cutaneous	90%
Urticaria and angioedema	85%-90%
Flushing	45%-55%
Pruritus without rash	2%-5%
Respiratory	40%-60%
Dyspnea, wheeze	45%-50%
Upper airway angioedema	50%-60%
Rhinitis	15%-20%
Dizziness, syncope, hypotension	30%-35%
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25%-30%
Miscellaneous	
Headache	5%-8%
Substernal pain	4%-6%
Seizure	1%-2%

*On the basis of a compilation of 1865 patients reported in references 1 through 14.
†Percentages are approximations.

73. Allergen immunotherapy with the appropriate stinging insect venom should be recommended for patients with systemic sensitivity to stinging insects because this treatment is highly (90% to 98%) effective.
74. Desensitization to medications that are known to have caused anaphylaxis can be effective. In most cases the effect of desensitization is temporary, and if the medication is required some time in the future, the desensitization process must be repeated.
75. Patient education might be the most important preventive strategy. Patients should be carefully instructed about hidden allergens, cross-reactions to various allergens, unforeseen risks during medical procedures, and when and how to use self-administered epinephrine. Physicians should educate patients about the risks of future anaphylaxis, as well as the benefits of avoidance measures.

EVALUATION AND MANAGEMENT OF THE PATIENT WITH A HISTORY OF EPISODES OF ANAPHYLAXIS

Summary Statements

1. The history is the most important tool to determine whether a patient has had anaphylaxis and the cause of the episode. **C**
2. A thorough differential diagnosis should be considered, and other conditions should be ruled out. **C**
3. Laboratory tests can be helpful to confirm a diagnosis of anaphylaxis or rule out other causes. Proper timing of studies (eg, serum tryptase is essential). **B**
4. In the management of a patient with a previous episode, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. **C**

TABLE II. Types of anaphylaxis and the differential diagnosis of anaphylaxis and anaphylactoid reactions

Types of anaphylaxis and anaphylactoid reactions
Anaphylaxis (anaphylactoid reactions) to exogenous agents
Anaphylaxis and anaphylactoid reactions to physical factors
Exercise
Cold
Heat
Sunlight
Idiopathic anaphylaxis
Anaphylaxis and anaphylactoid reactions caused by the excess endogenous production of histamine
Systemic mastocytosis
Urticaria pigmentosa
Basophilic leukemia
Acute promyelocytic leukemia with tretinoin treatment
Hydatid cyst
Vasodepressor (vasovagal) reactions
Other forms of shock
Hemorrhagic
Hypoglycemic
Cardiogenic
Endotoxic
Flushing syndromes
Carcinoid
Red man syndrome caused by vancomycin
Postmenopausal
Alcohol induced
Unrelated to drug ingestion
Related to drug ingestion
Medullary carcinoma thyroid
Autonomic epilepsy
Vasointestinal peptide and other vasoactive peptide–secreting gastrointestinal tumors
Ingestant-related reactions mimicking anaphylaxis (restaurant syndromes)
Monosodium glutamate
Sulfites
Scombroidosis
Nonorganic diseases
Panic attacks
Vocal cord dysfunction syndrome
Miscellaneous
C1 esterase deficiency syndromes (acquired and hereditary angioedema)
Pheochromocytoma
Neurologic (seizure, stroke)
Capillary leak syndrome

5. The patient should be instructed to wear and/or carry identification denoting his or her condition (eg, Medic Alert jewelry). **C**

Performing the history

To interpret the history adequately, it is essential to know the manifestations of anaphylaxis. These can best be ascertained by a review of published series.[1-14] A summary of the signs and symptoms as reported in these series, totaling 1865 patients, is seen in Table I. These series include patients with exercise-induced anaphylaxis, patients with idiopathic anaphylaxis, patients of all age ranges, and reviews of patients with anaphylaxis from various causes. The most frequent manifestations of anaphylaxis are cutaneous, occurring in more than 90% of reported series. The absence of cutaneous symptoms speaks against a diagnosis of anaphylaxis but does not rule it out. Severe episodes characterized by rapid cardiovascular collapse and shock can occur without cutaneous manifestations.[15,16] Friends and/or family members present during the event should be interviewed to better assess the signs and symptoms of the reaction. Anaphylaxis can present with unusual manifestations (eg, syncope without any other sign or symptom).[17,18]

The history and the record should include the time(s) of the occurrence of the attack(s), any treatment required during the attack(s), and the duration of the episode(s). A detailed history of all potential causes should be obtained. This includes a list of ingestants consumed before the event, including both foods and drugs; any possible stings or bites occurring before the event; whether the event occurred during exercise; location of the event (eg, work versus home); and whether the event was related to exposure to heat or cold or sexual activity. The patient's atopic status should be noted because food-induced and idiopathic anaphylaxis are more common in atopic than nonatopic individuals. Also, in women the history should include any relationship between the attack(s) and their menstrual cycle. Return of symptoms after a remission should be noted because this might indicate a late-phase reaction,[6] which might require a prolonged period of observation if subsequent events occur.

Differential diagnosis

The vast majority of patients presenting with a history consistent with anaphylaxis will have experienced an anaphylactic event. Nonetheless, it is important not to immediately accept this diagnosis. The differential diagnosis must be considered when the history is taken, even in patients with a previous history of anaphylaxis. Comprehensive differential diagnoses are seen in Table II.

Special attention in the differential diagnosis should be given to vasodepressor (vasovagal) reactions. Characteristic features of this reaction include hypotension, pallor, weakness, nausea, vomiting, and diaphoresis. Such reactions can often be distinguished from anaphylaxis by a lack of characteristic cutaneous manifestations (urticaria, angioedema, flush, and pruritus) and the presence of bradycardia during the vasodepressor reaction instead of the tachycardia usually seen with anaphylaxis. However, it should be noted that bradycardia can occur during anaphylaxis as well.[19] This is probably due to the Bezold-Jarisch reflex, a cardioinhibitory reflex that has its origin in sensory receptors in the inferoposterior wall of the left ventricle. Unmyelinated vagal C fibers transmit the reflex.

Flushing episodes can mimic anaphylactic events. As noted, the history should include all of the drugs that the

patient was taking before the event. Several drugs and ingestants, including niacin, nicotine, catecholamines, angiotensin-converting enzyme inhibitors, and alcohol, can induce flushing.[20] Other conditions that cause flushing must be considered, including gastrointestinal and thyroid tumors, the carcinoid syndrome, pheochromocytoma, hyperglycemia, postmenopausal flush, alcohol-induced flushing, and the red man syndrome caused by the administration of vancomycin. Laboratory analysis (see below) can be helpful in establishing the cause of flushing.

There are a group of postprandial syndromes that can mimic anaphylaxis, such as monosodium glutamate–induced reaction and reactions to scombroid fish (see ''Food allergy: a practice parameter''). The latter is increasing in frequency,[21] and because it is caused by histamine produced by histidine-decarboxylating bacteria that cleave histamine from histidine in spoiled fish, the symptoms can be identical to those that occur in anaphylaxis. However, the cutaneous manifestation can be more of a flush (sunburn-like) than urticaria. Symptoms might affect more than one individual if others also ingested the fish causing the reaction and serum tryptase levels are normal.

Nonorganic disease, such as vocal cord dysfunction and panic attacks, should be considered in the differential diagnosis.

Laboratory studies

Laboratory studies to be considered are shown in Table III. Serum tryptase and plasma and urinary histamine metabolites might be helpful in establishing the diagnosis of anaphylaxis.[22,23] Plasma histamine levels begin to increase within 5 to 10 minutes of the onset of symptoms of anaphylaxis and remain increased for 30 to 60 minutes.[24,25] Therefore they are not of help if the patient is seen as long as an hour or more after the onset of the event.[24] However, urinary methyl-histamine levels are increased for a longer duration of time.[26] Serum tryptase levels peak 1 to 1½ hours after the onset of anaphylaxis and can persist for as long as 5 hours after the onset of symptoms.[25] The best time to measure serum tryptase levels is between 1 to 2 hours but no longer than 6 hours after the onset of symptoms.[25] The best time to measure plasma histamine levels is between 10 minutes and 1 hour after the onset of symptoms.[25] It should be noted that there can be a disconnection between histamine and tryptase levels, with some patients exhibiting increase of only one of these mediators.[25]

There are 2 forms of tryptase, α and β.[22] α-Tryptase is secreted constitutively, and β-tryptase is released only during degranulation episodes. This observation is useful in distinguishing between systemic anaphylaxis per se and a degranulation of mast cells related to mastocytosis. The distinction between these 2 disorders rests on the fact that patients with mastocytosis, because of their increased mast cell burden, constitutively produce larger amounts of α-tryptase (compared with normal subjects), whereas patients who have true anaphylactic events of other causes will have normal baseline levels of α-tryptase. During anaphylactic events, β-tryptase is secreted in large amounts in both groups. Therefore the ratio of total tryptase (α plus β) to β-tryptase can be useful in distinguishing degranulation episodes in patients with mastocytosis from anaphylactic events in patients without this disorder. In addition, constitutively increased levels of α-tryptase are helpful in making a diagnosis of mastocytosis. A ratio of total tryptase (α plus β) to β-tryptase of 10 or less is indicative of an anaphylactic episode not related to systemic mastocytosis, whereas a ratio of 20 or greater is consistent with systemic mastocytosis.[22] This distinction is made possible because of the fact that the immunoassay for tryptase using a B12 mAb or a G4 mAb recognizes both α- and β-tryptase, whereas an assay using a G5 mAb recognizes only β-tryptase.[22]

It has been proposed that an increase of postmortem serum tryptase level be used to establish anaphylaxis as a cause of death.[27] However, it should be clearly noted that postmortem increase of serum tryptase concentrations is not a specific finding and therefore cannot be considered diagnostic of an anaphylactic death. There are reports detailing nonanaphylactic deaths exhibiting increased

TABLE III. Laboratory tests to be considered in the differential diagnosis of anaphylaxis

To be measured	Comment
Serum tryptase	Serum tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6 hours. Ideally, the measurement should be obtained between 1 and 2 hours after the initiation of symptoms.
Plasma histamine	Plasma histamine levels begin to increase within 5-10 min and remain increased only for 30-60 min. They are of little help if the patient is seen as long as an hour or more after the onset of the event.
24-h Urinary histamine metabolite (methyl histamine)	Urinary histamine and its metabolites are increased for a longer period of time, up to 24 hours.
Plasma-free metanephrine	To rule out a paradoxical response to a pheochromocytoma.
Urinary vanillylmandelic acid	Also useful in ruling out a paradoxical response to a pheochromocytoma.
Serum serotonin	To rule out carcinoid syndrome.
Urinary 5-hydroxyindoleacetic acid	Also to rule out carcinoid syndrome.
Serum vasointestinal hormonal polypeptide panel, including pancreastatin, pancreatic hormone, vasointestinal polypeptide (VIP), and substance P	Useful to rule out the presence of a vasoactive polypeptide secreting gastrointestinal tumor or a medullary carcinoma of the thyroid, which also can secrete vasoactive peptides.

postmortem serum tryptase levels.[28-30] Thus the presence of an increased postmortem tryptase level cannot be considered pathognomonic for a death caused by anaphylaxis or an anaphylactoid event. Neither can an absence of an increased serum tryptase level postmortem be considered sufficient to rule out anaphylaxis or an anaphylactoid event as the cause of death.[28]

In search of the culprit in patients with possible anaphylaxis to food, leftover or vomited food might be useful as a source of antigen for the creation of a custom RAST reagent.[27]

In the management of a patient with a previous episode, education is necessary, including emphasis on early treatment, specifically the self-administration of epinephrine. Patients who have experienced an episode of anaphylaxis should also be equipped with identification denoting their possible susceptibility to future episodes. This can consist of a card and/or identification jewelry (eg, Medic Alert).

Medical facilities should have an established protocol to deal with anaphylactic episodes and the appropriate equipment to treat the episode. In addition, telephone numbers for paramedical rescue squads and ambulance services should be on hand.

MANAGEMENT OF ANAPHYLAXIS

Summary Statements

6. Medical facilities should have an established protocol to deal with anaphylaxis and the appropriate equipment to treat the episode. In addition, telephone numbers for paramedical rescue squads and ambulance services might be helpful to have on hand. **B**
7. Anaphylaxis is an acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils. **B**
8. Anaphylactic (IgE-dependent) and anaphylactoid (IgE-independent) reactions differ mechanistically, but the clinical presentations are identical. **C**
9. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. **C**
10. Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. **C**
11. Any health care facility should have a plan of action for anaphylaxis should it occur. Physicians and office staff should maintain clinical proficiency in anaphylaxis management. **D**
12. Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis. **A/D**
13. Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital is essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting. **B**

Signs and symptoms of anaphylaxis

There is no universally accepted clinical definition of anaphylaxis.[31,32] Anaphylaxis is an acute life-threatening reaction that results from the sudden systemic release of mast cells and basophil mediators. It has varied clinical presentations, but respiratory compromise and cardiovascular collapse cause the most concern because they are the most frequent causes of anaphylactic fatalities.[32] Anaphylactic (IgE-dependent) and anaphylactoid (IgE-independent) reactions differ mechanistically, but the clinical presentations are identical. Anaphylaxis might affect the level of consciousness (impairment might reflect hypoxia), the upper and lower airways (dysphonia, stridor, cough, wheezing, or shortness of breath), the cardiovascular system (hypotension with or without syncope and/or cardiac arrhythmias), the skin (diffuse or localized erythema, pruritus, urticaria, and/or angioedema), and the gastrointestinal system (nausea, vomiting, or diarrhea). In addition, some patients might have symptoms of lightheadedness, headache, uterine cramps, feeling of impending doom, or unconsciousness.

Urticaria and angioedema are the most common manifestations of anaphylaxis[2,8,33] and often occur as the initial signs of severe anaphylaxis. However, cutaneous findings might be delayed or absent in rapidly progressive anaphylaxis. The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. Moreover, symptoms not immediately life-threatening might progress rapidly unless treated promptly and appropriately.

Anaphylaxis often produces signs and symptoms within seconds to minutes of exposure to an offending stimulus, but some reactions might develop later (eg, greater than 30 minutes after exposure). Late-phase or biphasic reactions, which occur 8 to 12 hours after the initial attack, have also been reported.[34-36] Some protracted reactions can last up to 32 hours, despite aggressive treatment.[35,36]

Increased vascular permeability, a characteristic feature of anaphylaxis, allows transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes.[37,38] As a result, hemodynamic collapse can occur rapidly, with little or no cutaneous or respiratory manifestations.[15,16]

Differential diagnosis in anaphylaxis

The differential diagnosis of anaphylaxis is reviewed elsewhere in this parameter (see ''Evaluation and management of the patient with a history of episodes of anaphylaxis'' and Table II). Like anaphylaxis, several conditions can cause abrupt and dramatic patient collapse. Among conditions to consider are vasodepressor (vasovagal) reactions, acute anxiety (eg, panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, systemic mast cell disorders, foreign-body aspiration, acute poisoning, hypoglycemia, and seizure disorder. Specific signs and symptoms of

anaphylaxis can present singly in other disorders. Examples are urticaria-angioedema, hereditary angioedema, and asthma.

The vasodepressor (vasovagal) reaction probably is the condition most commonly confused with anaphylactic and anaphylactoid reactions. In vasodepressor reactions, however, urticaria is absent, the heart rate is typically bradycardic, bronchospasm or other breathing difficulty is generally absent, the blood pressure is usually normal or increased, and the skin is typically cool and pale. Tachycardia is the rule in anaphylaxis, but it might be absent in patients with conduction defects, patients with increased vagal tone caused by a cardioinhibitory (Bezold-Jarisch) reflex, or patients who take sympatholytic medications.

It should be recognized that urticaria and angioedema might be part of the continuum of anaphylaxis but in isolation are not anaphylaxis.

Management of anaphylaxis

The management of anaphylactic and anaphylactoid reactions is identical. A sequential approach to management is outlined in Table I, and a sample treatment flow sheet is presented in Fig 1. The following equipment supplies should be available for the treatment of anaphylaxis in medical settings in which allergen immunotherapy is administered or in which other medications or biologic agents are administered by means of injection[39,40]: (1) stethoscope and sphygmomanometer; (2) tourniquets, syringes, hypodermic needles, and large-bore needles (14-gauge needles); (3) injectable aqueous epinephrine 1:1000; (4) equipment for administering oxygen; (5) equipment for administering intravenous fluids; (6) oral airway; (7) diphenhydramine or similar injectable antihistamine; (8) corticosteroids for intravenous injection; and (9) a vasopressor (eg, dopamine or norepinephrine). Glucagon, an automatic defibrillator, and a 1-way valve facemask with an oxygen inlet port (eg, Pocket-Mask or similar device) are other materials that some clinicians might find desirable, depending on the clinical setting.

Fig 2 provides a sample checklist to track supplies needed to treat anaphylaxis and expiration dates for medications-fluids. Not all items need to be present in each office.

Evaluation and treatment in a latex-safe environment is optimal for patients with concomitant latex allergy. It is important to stress that these steps are subject to physician discretion and that variations in sequence and performance rely on physician judgment. Additionally, when a patient should be transferred to an emergency facility depends on the skill, experience, and clinical decision making of the individual physician. Medical offices in which anaphylaxis is likely to occur (eg, in which allergen immunotherapy is administered) should consider periodic anaphylaxis practice drills tailored to local emergency medical service capabilities and response times. Essential ingredients to such drills are identification of a person who will be responsible for calling emergency medical services and a person who will document treatment and time each is rendered. The emergency kit should be up to date and complete. Everyone who will be directly involved in patient care should, for example, easily be able to locate necessary supplies and rapidly assemble fluids for intravenous administration.

Assessment and maintenance of airway, breathing, and circulation are necessary before proceeding to other management steps. Measurement of peak expiratory flow rate and pulse oximetry might be useful in patients with dyspnea, bronchospasm, or both. Epinephrine administration and the maintenance of adequate oxygenation and intravascular volume have high priority.

Epinephrine. Epinephrine is the treatment of choice for acute anaphylaxis.[31,41,42] Aqueous epinephrine 1:1000 dilution, 0.2 to 0.5 mL (0.01 mg/kg in children; maximum dose, 0.3 mg) administered intramuscularly or subcutaneously every 5 minutes, as necessary, should be used to control symptoms and increase blood pressure. Consider dose-response effects. *Note:* If the clinician deems it appropriate, the 5-minute interval between injections can be liberalized to permit more frequent injections.

Subsequent therapeutic interventions depend on the severity of the reaction and the initial response to epinephrine. No data support the use of epinephrine in anaphylaxis through a nonparenteral route. However, alternative routes of administration have been anecdotally successful. These include, for example, inhaled epinephrine in the presence of laryngeal edema or sublingual injection if an intravenous route cannot be obtained. Endotracheally administered dosages have also been proposed for use when intravenous access is not available in intubated patients experiencing cardiac arrest.[43]

Fatalities during anaphylaxis usually result from delayed administration of epinephrine and from severe respiratory complications, cardiovascular complications, or both. There is no absolute contraindication to epinephrine administration in anaphylaxis.[44,45]

Absorption is more rapid and plasma levels are higher in children not experiencing anaphylaxis who receive epinephrine intramuscularly in the thigh with an autoinjector.[46] Intramuscular injection into the thigh (vastus lateralis) in adults not experiencing anaphylaxis is also superior to intramuscular or subcutaneous injection into the arm (deltoid), neither of which achieves increased plasma epinephrine levels compared with endogenous levels.[47] Spring-loaded (eg, EpiPen) automatic epinephrine devices administered intramuscularly and intramuscular epinephrine injections through a syringe into the thigh in adults not experiencing anaphylaxis provide dose-equivalent plasma levels.[46,47] However, similar studies comparing intramuscular injections to subcutaneous injections in the thigh have not yet been done.

The UK consensus panel on emergency guidelines and the international consensus guidelines for emergency cardiovascular care both recommend intramuscular epinephrine injections for anaphylaxis.[31,41] Both publications also propose that epinephrine can be repeated every 5 minutes, as clinically needed, in both adults and children.[31,41] It seems reasonable to infer that the 5-minute

interval between injections can be liberalized to permit more frequent injections if the clinician deems it appropriate. Development of toxicity or inadequate response to epinephrine injections indicates that additional therapeutic modalities are necessary.

No established dosage or regimen for intravenous epinephrine in anaphylaxis is recognized. Inferences can be drawn from the emergency cardiac care consensus guidelines for intravenous epinephrine for adults and children.[41,48] An epinephrine infusion might be prepared by adding 1 mg (1 ml) of a 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4.0 μg/ml. This 1:250,000 solution is infused at a rate of 1 to 4 μg/min (15-60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10.0 μg/min for adults and adolescents. A dosage of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution up to 10 μg/min; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the ''rule of 6'' is as follows: 0.6 × body weight (in kilograms) = numbers of milligrams diluted to total 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min.[48] (See Table II for infusion guidelines in children.)

An alternative epinephrine infusion protocol has been suggested for adults with anaphylaxis. Brown and colleagues conducted a prospective, randomized, double-blind, placebo-controlled, crossover study of *Myrmecia pilosula* (jack jumper ant) venom immunotherapy in which 21 otherwise healthy adults experienced systemic reactions after diagnostic sting challenge.[19] Two individuals experienced urticarial reactions and received no epinephrine. The remaining 19 patients (8 of whom had systolic blood pressure of less than 90 mm Hg) received a 1:100,000 solution of epinephrine (1 mg [1 mL] in 100 mL of saline) intravenously by means of infusion pump at an initial rate of 30 to 100 mL/h (5-15 μg/min) titrated up or down depending on clinical response or epinephrine side effects (toxicity). This infusion was discontinued 30 minutes after resolution of all signs and symptoms of anaphylaxis.

Five of the 8 patients with hypotension also received a 1-L bolus of normal saline during the first few minutes of treatment. Eighteen of the 19 patients who received epinephrine infusions had symptomatic improvement and systolic blood pressures of greater than 90 mm Hg within 5 minutes. The remaining individual required an additional 2 L of saline (3 L total).

Note: Because of the risk for potentially lethal arrhythmias, epinephrine should be administered intravenously only during cardiac arrest or to profoundly hypotensive subjects who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations in which hemodynamic monitoring is available (eg, emergency department or intensive care facility), continuous hemodynamic monitoring is essential.[32] However, use of intravenous epinephrine should not be precluded in a scenario in which such monitoring is not available if the clinician deems its administration is essential after failure of several epinephrine injections in the thigh. If intravenous epinephrine is considered essential under these special circumstances, monitoring by available means (eg, every-minute blood pressure and pulse measurements and electrocardiographic monitoring) should be conducted.

H_1 and H_2 antagonists. Antihistamines (H_1 and H_2 antagonists) are supportive in the treatment of anaphylaxis. However, these agents have a much slower onset of action than epinephrine and should never be administered alone as treatment for anaphylaxis. Thus antihistamine use in anaphylaxis should be considered second-line treatment after the administration of epinephrine.

However, antihistamines are useful in the treatment of urticaria-angioedema or pruritus when they appear as manifestations of the anaphylactic episode. Diphenhydramine, 25 to 50 mg for adults and 1 mg/kg (up to 50 mg) for children, slowly might be administered intravenously. Oral diphenhydramine, in identical dosages, might be sufficient for milder attacks.

The role of H_2 antagonists, such as ranitidine and cimetidine, is more controversial, but several reports have demonstrated that a treatment with a combination of H_1 and H_2 antagonists is more effective in anaphylaxis than treatment with H_1 antagonists alone.[49-56] For example, an emergency department–based study involving 91 adult patients demonstrated that a combination of diphenhydramine and ranitidine provided superior resolution of cutaneous symptoms and tachycardia compared with diphenhydramine and saline.[55]

No controlled studies support use of one H_2 antagonist over another. Most studies have used either cimetidine or ranitidine. Ranitidine might be the drug of choice because it has fewer potential drug interactions. The recommended administration for ranitidine is 1 mg/kg in adults and 12.5 to 50 mg in children infused over 10 to 15 minutes.[57] Ranitidine also can be diluted in 5% dextrose to a total volume of 20 mL and injected over 5 minutes. Cimetidine, 4 mg/kg in adults, should be administered slowly because rapid intravenous administration might produce hypotension.[58] Cimetidine should not be administered to children with anaphylaxis because no dosages have been established.

Corticosteroids. Systemic corticosteroids have no role in the acute management of anaphylaxis because they might have no effect for 4 to 6 hours, even when administered intravenously. Although corticosteroids traditionally have been used in the management of anaphylaxis, their effect has never been evaluated in placebo-controlled trials. However, if their effects on other allergic diseases, such as asthma, are extrapolated, corticosteroids might potentially prevent protracted or biphasic anaphylaxis. They also form an essential part of the preventive management of frequent idiopathic anaphylaxis.[59] Corticosteroids administered during anaphylaxis might provide additional benefit for patients with asthma or other conditions recently treated with corticosteroids.[45]

If given, intravenous corticosteroids should be administered early in the treatment of anaphylaxis at a dosage equivalent to 1.0 to 2.0 mg/kg/d of methylprednisolone

every 6 hours. Oral administration of prednisone, 0.5 mg/kg, might be sufficient for milder attacks.

Oxygen and adrenergic agonists. Oxygen should be administered to patients with anaphylaxis who have prolonged reactions, have pre-existing hypoxemia or myocardial dysfunction, receive inhaled β_2-agonists, or require multiple doses of epinephrine. Arterial blood gas determination (where available) or continuous pulse oximetry should guide oxygen therapy where hypoxemia is a concern. Inhaled β_2-agonists, such as albuterol (0.5 mL or 2.5 mg of a 5% solution), might be administered for bronchospasm refractory to epinephrine.

Persistent hypotension–potential contributory factors and appropriate roles of volume replacement and vasopressors. Numerous cases of unusually severe or refractory anaphylaxis have been reported in patients receiving β-adrenergic blockers.[36,60-72] Although the pharmacology of provocation or exacerbation of bronchospasm with use of β-blockers is well known, the pharmacodynamics that contribute to greater risk for more serious anaphylaxis are not as widely recognized.[73,74] That β-blockade can influence the severity of anaphylaxis is supported by evidence from both human and animal studies.[73-78] Greater severity of anaphylaxis observed in patients receiving β-blockers might relate, in part, to a blunted response to epinephrine commonly administered to treat anaphylaxis.[73] Epinephrine might paradoxically worsen anaphylaxis through facilitating unopposed α-adrenergic and reflex vagotonic effects. In patients receiving β-blockers, increased propensity not only for bronchospasm but also decreased cardiac contractility with perpetuation of hypotension and bradycardia might exist.[78-80] For these reasons, β-blocker–related anaphylaxis might be more likely to be refractory to management. Evidence suggests that more serious anaphylaxis might also be promoted in the setting of β-blocker exposure because of the action of β-blockers on cyclic nucleotides, which can lead to heightened mediator release.[73,78] There are no epidemiologic studies that indicate that anaphylaxis occurs more frequently in patients receiving β-blockers. The observed risk for more serious anaphylaxis in patients receiving β-blockers has promoted caution regarding casual use of β-blockers in patients who might or will be exposed to an anaphylactogenic stimulus, including but not limited to (1) patients receiving allergen immunotherapy or undergoing immediate hypersensitivity skin testing,[81,82] (2) patients receiving infusion of radiographic contrast media,[75] and (3) patients with anaphylactic potential to hymenoptera venom.[64,73] Suspension of β-blocker treatment in such patients might be appropriate; however, in view of β-blocker withdrawal syndromes observed in selected cases and the clear benefits that will accrue from use of β-blockers in patients for whom these drugs are indicated,[63-65,83-85] this determination must be considered carefully from an individualized risk-benefit standpoint.

The contention that increased risk for more severe anaphylaxis with β-blockers also includes cardioselective agents is supported by reports of unusually severe anaphylaxis described in association with β_1-selective antagonists[60-64] and *in vitro* histamine release demonstrated with either β_1- or β_2-antagonists.[65,66] Systemic effects, including potential for bronchospasm and bradycardia, are well described with use of ophthalmic β-blockers.[86] For the above reasons, until more data are available, absence of greater risk for anaphylaxis with β-blocker exposure in patients receiving cardioselective or ophthalmic β-blockers cannot be assumed.

In summary, patients taking β-adrenergic antagonists might be more likely to experience severe anaphylactic reactions characterized by paradoxical bradycardia, profound hypotension, and severe bronchospasm. Use of selective β_1-antagonists does not reduce the risk of anaphylaxis because both β_1- and β_2-antagonists can inhibit the β-adrenergic receptor.

Epinephrine administered during anaphylaxis to patients taking β-adrenergic antagonists might be ineffective. In this situation both glucagon administration and isotonic volume expansion (in some circumstances up to 7 L of crystalloid are necessary) might be necessary.[72,87-89] Glucagon might reverse refractory bronchospasm and hypotension during anaphylaxis in patients receiving β-adrenergic antagonists by activating adenyl cyclase directly and bypassing the β-adrenergic receptor.[90] The recommended dosage for glucagon is 1 to 5 mg (20-30 μg/kg [maximum dose, 1 mg] in children) administered intravenously over 5 minutes and followed by an infusion (5-15 μg/min) titrated to clinical response. Protection of the airway is important because glucagon might cause emesis and risk aspiration in severely drowsy or obtunded patients. Placement in the lateral recumbent position might be sufficient airway protection for many of these patients.

Fluid resuscitation. Changes in vascular permeability during anaphylaxis might permit transfer of 50% of the intravascular fluid into the extravascular space within 10 minutes.[37,38] This effective shift of blood volume is countered by compensatory vasopressor mechanisms that involve the release of norepinephrine and epinephrine,[91] as well as activation of the angiotensin system.[92,93] Resulting increases in catecholamines might produce varied effects. Some patients during anaphylaxis experience abnormal increases in peripheral resistance (reflecting maximal vasoconstriction),[94] whereas others have decreased systemic vascular resistance, despite increased endogenous catecholamine levels.[91] These variable effects of internal compensatory mechanisms might explain why epinephrine injections sometimes fail to help in anaphylaxis. In contrast, these patients might respond to fluid replacement. (See Table IV for age-dependent criteria for hypotension, as defined by international consensus guidelines for pediatric advanced life support.)

The patient whose hypotension persists despite epinephrine injections should receive intravenous crystalloid solutions or colloid volume expanders. Of available crystalloid solutions, saline is generally preferred in distributive shock (eg, anaphylactic shock) because it stays in the intravascular space longer than dextrose and

TABLE IV. Special considerations for anaphylaxis in children[22]

A. When is it hypotension?

Age	Systolic blood pressure (mm Hg)
Term neonates (0-28 d)	<60
Infants (1-12 mo)	<70
Children (>1 y to 10 y)	<70 + (2× age in y)
Beyond 10 y	<90

B. Infusion rates for epinephrine and dopamine in children with cardiac arrest or profound hypotension

Medication	Dose range	Preparation*
Dopamine	2-20 μg/kg/min	6× body weight (in kg) = no. of mg diluted to total 100 mL of saline; then 1 mL/h delivers 1 μg/kg/min
Epinephrine	0.1 μg/kg/min	0.6× body weight (in kg) = no. of mg diluted to total 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min

*Infusion rates shown use the "rule of 6." An alternative is to prepare a more diluted or more concentrated drug solution on the basis of a standard drug concentration, in which case an individual dose must be calculated for each patient and each infusion rate as follows: $Infusion\ rate(mL/h) = (Weight[kg] \times Dose[\mu g/kg/\min] \times 60\ \min/h)/Concentration(\mu g/mL)$.

contains no lactate, which might potentially exacerbate metabolic acidosis. One to 2 L of normal saline might need to be administered to adults at a rate of 5 to 10 mL/kg in the first 5 minutes. Children should receive up to 30 mL/kg in the first hour. Adults receiving colloid solution should receive 500 mL rapidly, followed by slow infusion.[19] Large volumes are often required, but it might be appropriate to monitor patients with underlying congestive heart failure or chronic renal disease for signs of volume overload once the effective fluid deficit is replaced.

Vasopressors. Vasopressors, such as dopamine (400 mg in 500 mL of 5% dextrose), administered at 2 to 20 μg/kg/min and titrated to maintain systolic blood pressure greater than 90 mm Hg, should be administered if epinephrine injections and volume expansion fail to alleviate hypotension. (See Table II for pediatric dosing of dopamine.) Dopamine will frequently increase blood pressure while maintaining or enhancing blood flow to the renal and splanchnic circulation. A critical care specialist might need to be consulted for any patient with intractable hypotension.[95] These agents would not be expected to work as well in those patients who have experienced maximal vasoconstriction as their internal compensatory response to anaphylaxis.

After promising results in various animal models for cardiopulmonary resuscitation, vasopressin has been investigated for potential benefit in human cardiac arrest in 3 randomized controlled trials,[96-98] and one case report investigated its effects on hypotension in 2 adults who experienced insect sting anaphylaxis.[99] Wenzel et al[98] proposed that "vasopressin was superior to epinephrine in patients with asystole" on the basis of post hoc statistical analysis (1 of 29 statistical comparisons), did not correct statistically for multiple comparisons, and included no sensitivity analysis for 33 subjects excluded from analysis.[100] The other 2 randomized controlled trials concluded there were no significant differences in survival to discharge or neurologic function when vasopressin was compared with epinephrine in cardiac arrest.

In summary, high-quality randomized control trials performed to date have not demonstrated that vasopressin efficacy equals or exceeds that of epinephrine in clinical outcomes of treatment for cardiac arrest. No controlled studies have been performed to evaluate the potential efficacy of vasopressin alone in anaphylaxis or in combination with epinephrine.

Analysis of anaphylaxis outcomes and procedures

After treatment for any episode of acute anaphylaxis, the clinician should consider an analysis of event and possible precipitating cause, particularly with respect to those steps that could or should be done to prevent future episodes. (See "Anaphylaxis and immunotherapy" on prevention of anaphylaxis and specific scenario of anaphylaxis.) The clinical staff should also critique its approach to the management of anaphylaxis after each episode in regard to what worked well and what needs improvement.

Guide to physician-supervised management of anaphylaxis

I. Immediate intervention
   a. Assessment of airway, breathing, circulation, and adequacy of mentation
   b. Administer aqueous epinephrine 1:1000 dilution, 0.2 to 0.5 mL (0.01 mg/kg in children, max 0.3 mg dosage) intramuscularly or subcutaneously into the arm (deltoid) every 5 minutes, as necessary, to control symptoms and blood pressure. The arm permits easy access for administration of epinephrine, although intramuscular injection into the anterolateral thigh (vastus lateralis) produces higher and more rapid peak plasma levels compared with injections administered intramuscularly or subcutaneously in the arm. Similar studies comparing intramuscular injections with subcutaneous injections in the thigh have not yet been done. Although intuitively higher and more rapid peak plasma levels seen with intramuscular injection in the thigh would appear desirable, the clinical significance of these data is not known. Alternatively, an epinephrine autoinjector (eg, EpiPen [0.3 mg] or EpiPen Jr [0.15 mg]) might be administered through clothing into the lateral thigh. Repeat every 5 minutes as necessary (avoid toxicity). *Note:* Some guidelines suggest that the 5-minute interval between injections can be liberalized to permit more frequent injections if the clinician deems it appropriate. There is no absolute contraindication to epinephrine administration in anaphylaxis. However, several anaphylaxis fatalities have been attributed to injudicious use of intravenous epinephrine.

II. Subsequent measures that might be necessary depending on response to epinephrine
   a. Place patient in recumbent position and elevate lower extremities.
   b. Establish and maintain airway (endotracheal tube or cricothyrotomy can be performed if required and if clinicians are adequately trained and proficient).
   c. Administer oxygen at 6-8 L/min.
   d. Establish venous access.
   e. Use normal intravenous saline for fluid replacement. Might require large volumes of crystalloid (1-2 L of normal saline to adults can be administered at 5-10 mL/kg in first 5 minutes; children can receive up to 30 mL/kg in the first hour). If hypotension persists, rapid infusion of volume expanders (colloid-containing solutions) might be necessary.

III. Where appropriate, specific measures to consider after epinephrine injections
   a. An epinephrine infusion might be prepared by adding 1 mg (1 mL) of 1:1000 dilution of epinephrine to 250 mL of D5W to yield a concentration of 4.0 μg/mL. This solution is infused intravenously at a rate of 1 to 4 μg/min (15 to 60 drops per minute with a microdrop apparatus [60 drops per minute = 1 mL = 60 mL/h]), increasing to a maximum of 10.0 μg/min for adults and adolescents. If an infusion pump is available, an alternative 1:100,000 solution of epinephrine (1 mg [1 mL] in 100 mL saline) can be prepared and administered intravenously at an initial rate of 30 to 100 mL/h (5-15 μg/min), titrated up or down depending on clinical response or epinephrine side effects (toxicity). A dosage of 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution; maximum dose, 0.3 mg) is recommended for children. Alternative pediatric dosage by the ''rule of 6'' is as follows: 0.6 × body weight (in kilograms) = number of milligrams diluted to total 100 mL of saline; then 1 mL/h delivers 0.1 μg/kg/min. *Note:* Because of the risk for potentially lethal arrhythmias, epinephrine should be administered intravenously only during cardiac arrest or to profoundly hypotensive subjects who have failed to respond to intravenous volume replacement and several injected doses of epinephrine. In situations in which hemodynamic monitoring is available (eg, emergency department or intensive care facility), continuous hemodynamic monitoring is essential. However, use of intravenous epinephrine should not be precluded in a scenario in which such monitoring is not available if the clinician deems its administration is essential after failure of several epinephrine injections in the thigh. If intravenous epinephrine is considered essential under these special circumstances, monitoring by available means (eg, every-minute blood pressure and pulse measurements and electrocardiographic monitoring, if available) should be conducted.
   b. Diphenhydramine, 1-2 mg/kg or 25-50 mg/dose (parenterally).
   c. Consider ranitidine, 1 mg/kg, which can be diluted in 5% dextrose (D5W) to a total volume of 20 mL and injected intravenously over 5 minutes. Cimetidine (4 mg/kg) can be administered intravenously to adults, but no pediatric dosage in anaphylaxis has been established. *Note:* In the management of anaphylaxis, a combination of diphenhydramine and ranitidine is superior to diphenhydramine alone.
   d. For bronchospasm resistant to epinephrine, use nebulized albuterol, 2.5-5 mg in 3 mL of saline, and repeat as necessary.
   e. For hypotension refractory to volume replacement and epinephrine injections, dopamine, 400 mg in 500 mL D5W, can be administered intravenously at 2 to 20 μg/kg/min, with the rate titrated to maintain adequate blood pressure. Continuous hemodynamic monitoring is essential.
   f. Where β-blocker therapy complicates treatment, consider glucagon, 1-5 mg (20-30 μg/kg [maximum, 1 mg] in children), administered intravenously over 5 minutes followed by an infusion (5-15 μg/min). Aspiration precautions should be observed because glucagon can cause nausea and emesis.
   g. Consider systemic glucocorticosteroids for patients with a history of idiopathic anaphylaxis and asthma and patients who experience severe or prolonged anaphylaxis. Glucocorticosteroids usually are not helpful acutely, but potentially might prevent recurrent or protracted anaphylaxis. If given, intravenous steroids should be administered every 6 hours at a dosage equivalent to methylprednisolone (1.0-2.0 mg/kg/day). Oral administration of prednisone, 0.5 mg/kg, might be sufficient for less critical anaphylactic episodes.
   h. Consider transportation to the emergency department or an intensive care facility.

IV. Key additional interventions for cardiopulmonary arrest occurring during anaphylaxis
   a. Cardiopulmonary resuscitation and advanced cardiac life support measures.
   b. High-dose intravenous epinephrine (ie, rapid progression to high dose). A commonly used sequence is 1 to 3 mg (1:10,000 dilution) slowly administered intravenously over 3 minutes, 3 to 5 mg administered intravenously over 3 minutes, and then a 4 to 10 μg/min infusion. The recommended initial resuscitation dosage in children is 0.01 mg/kg (0.1 mL/kg of a 1:10,000 solution up to a maximum of 0.3 mg) repeated every 3 to 5 minutes for ongoing arrest. Another option is to start an epinephrine infusion and deliver up to 10 μg/min. Higher subsequent dosages (0.1-0.2

mg/kg; 0.1 ml/kg of a 1:1,000 solution) might be considered for unresponsive asystole or pulseless electrical activity. These arrhythmias are often observed during cardiopulmonary arrest that occurs in anaphylaxis.

c. Rapid volume expansion is mandatory.
d. Atropine and transcutaneous pacing should be considered if asystole and/or pulseless electrical activity are present.
e. Prolonged resuscitation efforts are encouraged, if necessary, because efforts are more likely to be successful in anaphylaxis when the patient is young and has a healthy cardiovascular system.
f. Transport to the emergency department or an intensive care facility, as the setting dictates.

VI. Observation and subsequent follow-up
a. Observation periods must be individualized because there are no reliable predictors of biphasic or protracted anaphylaxis on the basis of initial clinical presentation. Follow-up accordingly must be individualized and based on such factors as clinical scenario and distance from the patient's home to the closest emergency facility. After resolution of the acute episode, patients should be provided with an epinephrine syringe and receive proper instruction for self-administration in case of a subsequent episode. All individuals experiencing anaphylaxis require a careful history and targeted diagnostic evaluation in consultation with an allergist-immunologist.

ANAPHYLAXIS TO FOODS

Summary Statements

14. Severe food reactions have been reported to involve the gastrointestinal, cutaneous, respiratory, and cardiovascular systems. **D**
15. The greatest number of anaphylactic episodes in children has involved peanuts, tree nuts (ie, walnuts, pecans, and others), fish, shellfish, milk, and eggs **(C)**. The greatest number of anaphylactic episodes in adults is due to shellfish **(C)**. Clinical cross-reactivity with other foods in the same group is unpredictable **(B)**. Additives can also cause anaphylaxis **(C)**.
16. Anaphylactic reactions to foods almost always occur immediately. Symptoms might then subside only to recur several hours later. **A**
17. The most useful diagnostic tests include skin tests and food challenges. *In vitro* testing with foods might be appropriate as an alternative screening procedure. **C**
18. Double- or single-blind placebo-controlled food challenges can be done in patients with suspected food allergy in a medical facility by personnel experienced in performing the procedure and prepared to treat anaphylaxis. **B**
19. Patient education should include discussion about avoidance and management of accidental ingestion. **C**
20. Schools might present a special hazard for the student with food allergy. Epinephrine should be available for use by the individuals in the school trained to respond to such a medical emergency. **C**

The true incidence of fatal or near-fatal anaphylaxis to food is unknown. One estimate, about a thousand severe episodes per year, has been extrapolated from emergency department reporting.[101] In 3 recent surveys food allergy was reported to be the most commonly identified cause of anaphylaxis, accounting for 35% to 55% of cases.[2,3,102]

Severe adverse food reactions can involve several major systems. Respiratory manifestations might include oral and pharyngeal swelling, hoarseness and laryngeal edema, wheezing, cough, breathlessness, and/or chest tightness. Cardiovascular manifestations might include cardiac ischemia, arrhythmias, and hypotension, which might produce loss of consciousness. Gastrointestinal signs and symptoms include nausea, bloating, diarrhea, and severe abdominal pain. It should be noted that in some female subjects, abdominal pain involves the lowest portion of the abdomen and might be due to uterine contractions. Cutaneous manifestations have included urticaria, angioedema, and erythema. Angioedema and erythema can occur without urticaria. Angioedema of the eyelids and involvement of the conjunctiva is possible. Individuals might also experience a metallic taste and a sense of impending doom.

Etiology

Many foods have been reported to cause anaphylaxis.[103,104] The greatest number of anaphylactic reactions to foods in the United States have been reported after exposure to peanuts, tree nuts, milk, and eggs in children, and shellfish, peanuts, and fish in adults.[105-108]

It should not be assumed that a reaction to one member of a food family necessarily incriminates any or all other members.[109-111] Certain foods contain epitopes that cross-react immunologically (eg, peanut and soy) but might not cross-react in terms of the clinical response.[112]

History

Obtaining a thorough history from patients who have experienced a life-threatening reaction that might have been caused by a food is crucial. The history might be unequivocal, as in the individual who eats a single food (eg, peanut) and shortly thereafter has anaphylaxis. It should be remembered that highly sensitive patients might experience anaphylaxis after inhalation (eg, cooking fish) exposure. However, in many patients with anaphylaxis, a food offender cannot be immediately identified. If anaphylaxis occurs repeatedly and food allergy is suspected, it might be possible to assemble a list of ingredients from foods associated with these events by searching for common constituents.[104]

The time from ingestion to symptom onset in food allergy is typically rapid, usually within minutes, but might be delayed up to an hour and in some instances up to a few hours.[111,113] Symptoms might then subside only to recur several hours later (biphasic reaction).

Fatal food anaphylaxis might begin with mild symptoms, sometimes involving the skin, and then progress to shock with cardiovascular collapse over a 1- to 3-hour period.[107]

In evaluating suspected food allergy, it is important to consider associated factors, such as exercise after food ingestion (see section on exercise-induced anaphylaxis and ''Food allergy: a practice parameter'').[13]

Diagnostic testing

Presently, the most useful diagnostic tests for food allergy include skin tests, *in vitro* serum specific IgE assays, and oral food challenges. The test of choice is the skin test. It should be recognized that although many food allergens have been well characterized, standardized food extracts are not currently available, and skin tests might need to be performed to fresh food extracts.[103] If skin testing is done, the challenge solution should be diluted, and testing should be performed by a physician experienced in the procedure in a setting with appropriate rescue equipment and medications available. In certain instances *in vitro* serum specific IgE determinations can be helpful.

Food challenges

The degree to which the history and diagnostic testing confirm that a single specific food is responsible for the reaction that the patient has experienced will determine the need for a food challenge. If the history and diagnostic testing give an unequivocal answer, no challenge is necessary. Inadvertent ingestion of a food will often confirm that the initial suspicion about that food was correct.

However, if a definite food has not been identified as the cause of the reaction but foods are still suspected, food challenge might be necessary because identification of the food might be life-saving.[107] Double- or single-blind placebo-controlled food challenges can be performed safely in individuals with a history of food-induced anaphylaxis.[104-108] Open and nonblinded challenge can also be performed. It might be especially helpful when it is unlikely that the suspect food was responsible for the reaction and the patient needs to be reassured that it is safe to ingest the particular agent used. However, it might be necessary to begin with a minute amount of the suspected food, and the challenge should be stopped when the first symptoms occur. Often, but not always, pruritus of the oral tissues or nausea is the initial complaint after challenge with the suspected food. It is important to remember that even a small amount of food allergen can precipitate anaphylaxis.[103]

Patient education

Education regarding avoidance and management of accidental ingestion of foods known to produce anaphylaxis is crucial because neither presently available medications nor immunotherapy has been shown to consistently prevent such reactions, and epinephrine has not always been effective in reversing anaphylaxis. In addition to attempting to identify the food that is causing anaphylaxis, it is important to teach patients about situations in which accidental ingestion might occur.[114-116]

Patients with food hypersensitivity should be taught to effectively read and interpret labels on foods and to inquire about ingredients in restaurant meals. In addition, patients should be educated about foods that might cross-react with the identified offender (eg, various shellfish). There are educational materials available from dietitians, as well as organizations such as the Food Allergy Network (10400 Eaton Place, #107, Fairfax, VA 22030-2208; phone, 703-691-3179; fax, 703-691-2713). Fortunately, the food industry is becoming more responsive about labeling of food allergens and providing information to the public about accidental contamination of food products with known allergens.

Exposure to foods at school, daycare, camps, and restaurants constitutes a special hazard for individuals with food allergy. If a child has a history of severe reactions to foods, the foods that caused the reaction should be identified for school personnel. School personnel should be informed about a student's history of anaphylaxis and the specific food (or foods) to which the child is allergic. An allergen-free environment should be constructed for the child at mealtime to prevent inadvertent ingestion such as might occur with shared food. There should be a written response plan available that can be initiated immediately if a reaction occurs. Unfortunately, not all school policy allows children to have ready access to epinephrine at school. However, youngsters allergic to foods are covered by the Americans with Disabilities Act, which should make it easier to arrange an emergency medical response for accidental severe food reactions. Individuals with a history of a life-threatening reaction to a food should carry epinephrine. This includes individuals who have had any respiratory symptoms or a decrease in blood pressure during a reaction to a food. Patients at risk should carry identification, such as a Medic Alert jewelry.

If epinephrine is prescribed for the patient, the patient must understand that it should be available at all times. This instruction might require constant reinforcement. Compliance is more likely in young children, for whom adults are responsible. Compliance is the most difficult in adolescents and young adults. If a reaction is of such severity that epinephrine is required, the patient should be transported to the nearest emergency facility by ambulance for monitoring after epinephrine has been administered.

Ongoing evaluation

It is recommended that patients be instructed in the importance of reporting any and all anaphylactic reactions to their physician as soon as possible after they occur. If the exact cause of these reactions has not been identified, discussing the reaction with the physician while it is still

fresh in the patient's mind might help to define the specific food causing the reaction. If the cause of the patient's reactions is known, this interaction can re-establish that the food responsible for these reactions was correctly identified and that the appropriate treatment response was initiated.

LATEX-INDUCED ANAPHYLAXIS

Summary Statements

21. Latex (rubber) hypersensitivity is a significant medical problem, and 3 groups are at higher risk of reaction: health care workers, children with spina bifida and genitourinary abnormalities, and workers with occupational exposure to latex. **B**
22. Skin prick tests with latex extracts should be considered for patients who are members of high-risk groups or who have a clinical history of possible latex allergy to identify IgE-mediated sensitivity. Although a standardized commercial skin test reagent for latex is not available in the United States, many allergy centers have prepared latex extracts from gloves to be used for clinical testing. It should be noted, however, that such extracts, prepared from gloves, demonstrate tremendous variability in the content of latex antigen. *In vitro* assays for IgE to latex might also be useful, although these tests are generally less sensitive than skin tests. **C**
23. Patients with spina bifida (regardless of a history of latex allergy) and other patients with a positive history of latex allergy ideally should have all medical-surgical-dental procedures performed in a latex-safe environment and as the first case of the day. **D**
24. A latex-free environment is an environment in which no latex gloves are used in the room or surgical suite and no latex accessories (catheters, adhesives, tourniquets, and anesthesia equipment) come into contact with the patient. **D**
25. In health care settings general use of latex gloves with negligible allergen content, powder-free latex gloves, and nonlatex gloves and medical articles should be considered in an effort to minimize exposure to latex allergen. Such a combined approach might minimize latex allergen. Such a combined approach might minimize latex sensitization of health care workers and patients and should reduce the risk of inadvertent reactions to latex in previously sensitized individuals. **C**

Latex sensitization caused by IgE mast cell–mediated reactivity to any or a number of antigens from *Hevea brasiliensis*, the source of latex, occurs in a significant percentage of the health care worker population,[117] up to 75% of the spina bifida population,[118,119] and in the population undergoing multiple surgical procedures. Sporadic cases of latex-induced anaphylaxis have been reported because of hair glue and plastic balls with latex pits.[120,121] An incidence of up to 6.5% of the general population has been noted to have detectable IgE to latex.[122] Atopic and latex-exposed individuals are also at higher risk of latex sensitization. Individuals might be sensitized to minor or major antigens. No more than 240 separate polypeptides can be discerned by means of 2-dimensional electrophoresis of latex cap. Less than 25% of these react with IgE from patients with latex allergy. These tend to cluster into groups of 11 proteins.[123] With exposure, sensitized individuals might experience urticaria, angioedema, rhinitis, bronchospasm, and anaphylaxis.

Incidence

Latex-induced anaphylaxis can present in the operating room in patients, surgeons, nurses, or anesthesiologists. Latex has been reported to account for up to 17% of cases of intraoperative anaphylaxis.[123]

Clinical findings

The features of intraoperative anaphylaxis from latex might differ considerably from latex-induced anaphylaxis not associated with surgical procedures. Although cutaneous, hypotensive, and respiratory events occur in both, hypotensive cardiovascular collapse is a feature of surgical reactions, and dizziness or syncope might be found largely in anaphylaxis induced by nonsurgical procedures.[124] In some situations anaphylaxis might not be IgE mediated, such as those caused by radiocontrast media, but it has become clear that latex-induced anaphylaxis is due to IgE mast cell–mediated mechanisms. Thus after a careful history and physical examination, detection of IgE to latex is quite helpful in the diagnosis. Unfortunately, no commercially available skin test reagent is available in the United States. For this reason, other materials, such as latex glove extracts, are often used. It should be noted that such extracts are not standardized, and the amount of latex allergen within these extracts is highly variable. Latex ELISA or CAP are also available, but because of the variability in the antigen response, the *in vitro* tests have highly variable sensitivity and specificity characteristics. The sensitivity has been found to be as low as 50% to as high as 100%.[125,126]

Latex-induced anaphylaxis might occur in a variety of situations, all involving direct contact with latex devices, usually gloves, or instruments or with aerosolization of latex antigen adhered to the cornstarch donning powder of latex gloves. Thus latex-induced reactions can occur with operative procedures when gloves are donned. Latex-induced reactions might occur immediately with latex contact or might be delayed from 30 to 60 minutes. Intraoperative latex-induced anaphylaxis might be related to the administration of drug through a latex port before surgery or during the surgical procedure itself. Latex-induced reactions have also been reported to occur during dental procedures from latex glove or dams, during obstetric or gynecologic examinations, during latex condom use, and from blowing into rubber balloons. Patients with spina bifida are potentially at risk at each surgical procedure because of the numbers of procedures they undergo.

Treatment

Latex-induced anaphylaxis is an IgE mast cell–mediated reaction and should be treated as any other case of anaphylaxis (see section on management of anaphylaxis, beginning on page S500).

Prevention

As aerosolization, inhalation, or direct contact with latex devices or latex antigen is the event resulting in the allergic response, and avoidance is clearly the prime mode of therapy. For the sensitive health care worker, latex gloves should not be worn, and the worker's colleagues should wear nonpowdered latex or nonlatex gloves. The workplace should be latex safe, with all nonglove latex devices replaced by nonlatex devices. A latex-free emergency cart (Table V) should be available to treat reactions. Although it is unclear whether rubber stopper vials can cause anaphylaxis, they should be avoided.

Latex precautions should be instituted when a latex-sensitive patient undergoes a surgical procedure, an obstetric or gynecologic examination, or dental care. The surgical room, dental area, or examination area should be free of latex devices. No latex gloves should be used, and the patient should be the first case of the day. Appropriate emergency medications must be available for treatment should a reaction occur. With these measures, latex-induced anaphylaxis should be markedly reduced.

It is important to recognize that cross-reactivity between latex and foods can occur. The commonly reported cross-reactive foods include banana, avocado, kiwi, and chestnut (see ''Food allergy: a practice parameter'').

TABLE V. Example of contents of latex-free cart

I.	Glass syringes
II.	Ampules
III.	Tubing without ports (taped ports)
IV.	Stopcocks
V.	Nonlatex stethoscope
VI.	Nonlatex gloves
VII.	Nonlatex breathing system
	Neoprene bags
	Plastic masks
	Nonlatex Ambu
	Uncuffed polyvinyl chloride endotracheal tube
VIII.	Dermicel
IX.	Disposable nonlatex blood pressure cuffs
	Webril tourniquets

ANAPHYLAXIS DURING GENERAL ANESTHESIA, THE INTRAOPERATIVE PERIOD, AND THE POSTOPERATIVE PERIOD

Summary Statements

26. The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4000 to 1 in 25,000. Anaphylaxis during anesthesia can present as cardiovascular collapse, airway obstruction, flushing, and/or edema of the skin. **C**
27. It might be difficult to differentiate between immune and nonimmune mast cell–mediated reactions and pharmacologic effects from the variety of medications administered during general anesthesia. **B**
28. Thiopental allergy has been documented with skin tests. **B**
29. Neuromuscular blocking agents, such as succinylcholine, can cause nonimmunologic histamine release, but there have been reports of IgE-mediated mechanisms in some cases. **B**
30. Reactions to opioid analgesics are usually caused by direct mast cell–mediator release rather than IgE-dependent mechanisms. **B**
31. Antibiotics that are administered perioperatively can cause immunologic or nonimmunologic generalized reactions. **B**
32. Protamine can also cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms. **B**
33. Latex is a potent allergen, and IgE-mediated reactions to latex during anesthesia have been clearly documented. Patients with multiple surgical procedures (eg, patients with spina bifida) and health care workers are at greater risk of latex sensitization. Precautions for latex-sensitive patients include avoiding the use of latex gloves and latex blood pressure cuffs, as well as latex intravenous tubing ports and rubber stoppers from medication vials. **B**
34. Blood transfusions can elicit a variety of systemic reactions, some of which might be IgE mediated or mediated through other immunologic mechanisms. **B**
35. Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions, although no IgE mechanism has yet been documented. **C**
36. The evaluation of IgE-mediated reactions to medications used during anesthesia can include skin testing to a variety of anesthetic agents. **B**
37. The management of anaphylactic or anaphylactoid reactions that occur during general anesthesia is similar to the management of anaphylaxis in other situations. **B**

Anaphylaxis or anaphylactoid reactions occur in 1:5000 to 1:25,000 general anesthetic administrations.[1] The mortality from anaphylaxis related to anesthesia is estimated to be as high as 6%. The multiple physiologic changes occurring before and during general anesthesia might limit or delay recognition of anaphylaxis. Signs of anaphylaxis include flushing or urticaria, hypotension, difficulty with intubation caused by laryngeal edema or increased ventilatory pressure, or inability to ventilate because of bronchospasm. Serum tryptase quantification during or immediately after a presumed anaphylactic or anaphylactoid event might be helpful in confirming clinical suspicion, particularly if a postevent sample demonstrates a decrease to normal value after the event.[1]

The causes of anaphylaxis or anaphylactoid reactions related to anesthesia are listed in order of approximate frequency of occurrence.[127-129]

- Muscle relaxants
- Latex
- Antibiotics, particularly β-lactam antibiotics
- Induction agents or hypnotics
- Opioids
- Colloids, particularly dextran, mannitol, or hydroxyethyl starch
- Blood products
- Others, including protamine, isosulfan blue dye for lymph node dissection, gelatin solution used for hemostasis, chlorhexidine, ethylene oxide, radiocontrast media, streptokinase, methylmethacrylate, chymopapain[130-133]

The rank order of occurrence is based on reviews for anesthesia during general surgery, but specific surgical procedures might differ with respect to likely cause.[127,128] For example, in cardiovascular surgery anesthesia-induced anaphylaxis is more likely caused by cephalosporins, gelatin solution, or protamine allergy rather than muscle relaxants.

Muscle relaxants are responsible for more than 60% of reactions during general anesthesia.[127,128,134,135] Most reactions occur because of direct mast cell activation, but life-threatening reactions are usually caused by specific IgE.[127,128] The shared tertiary or quaternary ammonium group results in cross-reactions among the muscle relaxants.[127,129] Succinylcholine might be more likely to cause reactions caused by flexibility of the molecule facilitating the cross-linking of specific IgE on mast cell or basophil membranes. Skin testing to specific dilutions of muscle relaxants has been useful in determining the safest agent after a suspected reaction.[136]

Natural rubber latex sensitivity is the second most common cause of perioperative anaphylaxis in some series. The incidence might be decreasing with time. Anaphylaxis caused by latex is more likely to be delayed or occur later during the procedure compared with that caused by muscle relaxants or induction agents. Multiple prior surgical procedures are a risk factor. A US Food and Drug Administration–approved *in vitro* test for latex-specific IgE is available, although false-negative results occur. A standardized skin-testing reagent is not available in the United States but is in Canada. Latex precautions are indicated if latex sensitivity is confirmed or highly suspected. Ideally, latex-safe operative suites should be available. If this is not an option, scheduling the anesthesia and procedure as the first case of the day and avoiding the use of latex products is suggested. Premedication regimens, usually including corticosteroids and combinations of antihistamines, might lessen the severity but have not been shown to prevent anaphylactic reactions.

Hypnotic induction agents are the third most likely cause of anesthesia anaphylaxis. Intravenous barbiturates have most commonly been responsible, but the reaction rate is probably less than 1:25,000, with the reported occurrence reflecting the common use of barbiturates. Mixing intravenous barbiturates with neuromuscular blocking agents in the same intravenous line might increase the likelihood of reactions. Skin testing has been reported with thioamyl and thiopental at 0.01 and 0.2 mg/mL, respectively.[137] Propofol is a nonbarbiturate induction agent and is useful if sensitivity to barbiturates is suspected. Specific IgE to propofol occurs, but most propofol reactions are due to direct mast cell activation.[138]

Narcotics used in anesthesia commonly cause flushing and urticaria after intravenous administration. The risk of anaphylaxis or anaphylactoid reactions, in contrast, is very rare.[139] Reducing the rate of opioid administration usually limits the severity of these reactions. Fentanyl does not directly stimulate histamine release through the mast cell opioid receptor.

Antibiotics are frequently administered before, during, or immediately after anesthesia and surgery. The most commonly implicated antibiotics resulting in reactions are β-lactams or vancomycin. IgE-mediated reactions occur in 0.04% to 0.015% of penicillin-treated subjects, and anaphylaxis occurs in approximately 0.001%. Intravenous administration of penicillin results in the most severe forms of anaphylaxis. Penicillin skin testing is useful to identify specific IgE. The sensitivity of penicillin skin testing is approximately 97% if aqueous penicillin and penicillin major determinant (Pre-pen) are used. The lack of a commercially available minor determinant, sensitivity to which can be associated with severe reactions, is an impediment. Percutaneous, followed by intracutaneous, testing with concentrations of up to 3 mg/mL for aqueous penicillin and 6×10^{-5} molar for major determinant are recommended to exclude penicillin allergy. *In vitro* testing for the major determinant is also available, but its negative predictive value is less well established and is less compared with immediate hypersensitivity testing.[140] Skin testing with penicillin derivatives or cephalosporins is not as well studied. Maximum testing concentrations of 1 to 3 mg/mL have been suggested for these other β-lactams. Carbapenems do not cross-react immunologically with penicillin. Desensitization schedules are available to facilitate use of β-lactam antibiotics, if absolutely necessary, in subjects with documented or suspected allergy. Vancomycin is a glycopeptide antibiotic selectively used for treatment of resistant organisms and for individuals with penicillin allergy. Administration, particularly rapid administration, might result in life-threatening anaphylactoid reactions. Evidence for both direct histamine release and direct myocardial depression partially explains this phenomenon. These nonimmunologic reactions to vancomycin can be reduced or eliminated by administration of a dilute solution, dissolved in at least 200 mL, that is slowly infused. Anaphylactic reactions to vancomycin occur but are much less common than anaphylactoid reactions. Skin testing with a concentration of up to 0.15 mg/mL has been reported, but the reliability of this testing is less secure than with penicillin. Skin testing might be of some value in distinguishing rate-related anaphylactoid reactions from anaphylaxis.

Intravenous protamine used to reverse heparin anticoagulation might cause anaphylactic or anaphylactoid reactions. The latter reactions are characterized by an increase in pulmonary blood pressure. Proposed causes include both immunologic and nonimmunologic mechanisms. A case-control study showed that prior neutral protamine Hagedorn insulin use (odds ratio, 8.18 [2.08,32.2]), fish allergy (odds ratio, 24.5 [1.24,482.3]), and other medication allergy (odds ratio, 2.97 [1.25,7.07]) are independent risk factors.[141] Estimates are that up to 39% of patients undergoing cardiopulmonary bypass have one or more of these risk factors. Alternative agents might be used for heparin reversal, but these are not readily available. Pretreatment regimens with corticosteroids and antihistamines have been recommended, but no studies confirm efficacy.

Dextran and hydroxyethel starch (HES), large-molecular-weight polysaccharides, might be used as a nonblood product and for high oncotic fluid replacement during surgery. These agents are rarely associated with adverse reactions, probably anaphylactoid, because of complement activation. Estimates of reaction rates are 0.008% to 0.08% for dextran and 0.08% for HES. Specific antibodies can be detected for dextran and HES, but the clinical significance of these is unknown. Confirmation of dextran or HES as the cause of an adverse reaction is limited by the absence of accurate serologic or skin tests. Skin test reactivity to undiluted solutions has been described but again is of unknown significance.[142]

Case reports are also in the literature describing systemic reactions to albumin. Details are not available as to the mechanism of the adverse effects.

The ideal of preventing perianesthetic reactions is elusive because of the rare occurrence of reactions; the multiple pathophysiologic mechanisms, many of which are undefined; and the limited ability to test for risk or sensitization.[143] A careful medical history focusing on prior adverse reactions is most important. Any prior medication reactions nonspecifically increase the possibility of adverse reactions, and multiple previous medication reactions are a greater risk. Atopic subjects might be at heightened risk, either because of increased occurrence of reactions or, more often, increased severity of reactions. Asthma should be stabilized with lung function maximized and bronchial hyperreactivity minimized, if possible. β-Blocker therapy is a risk factor that ideally should be avoided. Previous anesthetic associated reactions should be evaluated thoroughly with specific testing if indicated. IgA-deficient subjects should receive washed red blood cells and no whole blood to avoid exposure to exogenous IgA. Intraoperative antibiotic administration should be at a slow rate with careful hemodynamic monitoring. Drugs with histamine-releasing properties, for example morphine, d-tubocurarine, vancomycin, or quaternary muscle relaxants, should be administered as slowly as possible, particularly in subjects with asthma or cardiopulmonary disease. Risk factors for latex hypersensitivity should be reviewed and consideration given to testing for specific IgE if any risk factors are identified. Pretreatment regimens, as used for radiocontrast anaphylactoid reactions, have not been proved to prevent perianesthetic reactions but might reduce the severity of such reactions.

Local anesthetics

Adverse effects from local anesthetics are not uncommon, but immunologic mediated reactions after parenteral administration are very unusual. The usual cause of a local anesthetic reaction is a vasovagal response, anxiety, toxic complications, or an idiosyncratic reaction. Toxic effects usually result from inadvertent, systemic, high-dose administration. Systemic toxicity includes central nervous system stimulation or suppression and cardiac suppression with peripheral vasodilation. Epinephrine mixed with local anesthetics might contribute to the sensation of anxiety if systemic absorption occurs. IgE-mediated reactions to local anesthetics are exceedingly rare.[144]

SEMINAL FLUID–INDUCED ANAPHYLAXIS

Summary Statements

38. Anaphylaxis caused by human seminal fluid has been shown to be due to IgE-mediated sensitization by proteins of varying molecular weight. **B**
39. Localized seminal plasma hypersensitivity has been well described and is likely IgE mediated on the basis of successful response to rapid seminal plasma desensitization. **C**
40. History of atopic disease is the most consistent risk factor. However, anecdotal case reports have been associated with gynecologic surgery, injection of anti-RH immunoglobulin, and the postpartum state. **C**
41. The diagnosis is confirmed by means of skin and/or *in vitro* tests for serum-specific IgE by using proper reagents obtained from fractionation of seminal fluid components. **C**
42. Prevention of reactions to seminal fluid can be accomplished by barrier use of condoms. **C**
43. Immunotherapy to properly fractionated seminal fluid proteins has been universally successful in preventing anaphylaxis to seminal fluid, provided the sensitizing seminal fluid fractions are used as immunogens. Successful intravaginal graded challenge with unfractionated seminal fluid has been reported in a few cases, but the duration of protection is unknown. **C**
44. Localized and/or systemic seminal plasma hypersensitivity is not associated with infertility. **D**

Diagnosis

Anaphylaxis caused by coital exposure to human seminal fluid is a rare occurrence. Since the initial report in 1958, approximately 30 cases of seminal fluid–induced anaphylaxis have been described.[145-147] All reactions have occurred in female patients during or after sexual intercourse. The vast majority of such reactions are caused

by IgE-mediated sensitization to human seminal plasma proteins with molecular weights ranging from 12 to 75 kd.[148-150] In rare cases spermatozoa have been identified as the source of allergens inducing a cell-mediated reaction.[151] Coital anaphylaxis has also been attributed to exposure to exogenous allergens transferred through semen during sexual intercourse. Such unusual reactions occur when a male partner ingests a food (eg, walnuts) or drug (eg, penicillin) to which there is established sensitization in the female partner.[152,153] Human anaphylaxis has also been described after repetitive coital exposure to canine seminal plasma.[154]

Seminal plasma hypersensitivity is essentially a diagnosis by exclusion. A detailed history is essential to rule out underlying causes, such as sexually transmitted diseases, latex sensitivity, or transfer of food or drug proteins from the male sexual partner to the female who might be sensitized to these agents or other contactants, such as fragrant sanitary napkins. Seminal plasma protein anaphylaxis begins within seconds to minutes after ejaculation and presents with a range of symptoms, including the following: diffuse pruritus and urticaria; pelvic pain associated with uterine contractions; nasal symptoms, including rhinorrhea and sneezing; wheezing, dyspnea, and/or laryngeal edema; and, rarely, hypotension and syncope. The effective prevention of reactions by correct use of condoms is a common feature.[155] Failure of condoms to prevent anaphylaxis suggests either incorrect condom technique or concurrent sensitization to latex.[156] Localized vulvar and vaginal burning might occur as isolated symptoms or in conjunction with itching and swelling after ejaculation. There is no evidence to support the contention that localized vaginal seminal plasma hypersensitivity increases susceptibility of the individual to have future systemic anaphylactic symptoms.

The most significant risk for seminal plasma protein anaphylaxis is in patients with a history of allergic asthma or atopic dermatitis.[146,150,157,158] However, anecdotal case reports of seminal fluid–induced anaphylaxis have occurred postpartum, after gynecologic surgery, and after injection of anti-Rh immune globulin.[146] It has not been established whether such events are coincidental or could somehow modulate immune tolerance, resulting in sensitization to seminal fluid proteins. Reactions have also been observed in women whose male partners have recently undergone prostatectomy or vasectomy.[159] Anaphylactic events have been reported in women with multiple previous sexual encounters or in others after the first coital act.[146] Postcoital allergic reactions are not specific to one partner and almost always recur with different male partners. Surveys have indicated that most subjects with seminal plasma hypersensitivity are not generally promiscuous in that they typically have reported a history of less than 2 sexual partners.[146]

The diagnosis must be confirmed by means of demonstration of sensitization to seminal fluid proteins through *in vivo* and/or *in vitro* immunologic methods. Demonstration of increased serum specific IgE assays with both positive and negative control sera confirms sensitization.[149] On the basis of available data, *in vitro* tests (eg, RAST and ELISA) of serum specific IgE appear to be less sensitive than skin testing and could be due to the lack of reliable test allergens.[146] Thus a negative serologic test result for seminal plasma specific IgE does not exclude sensitization.

Because sensitive specific IgE assays are not readily available, skin prick testing with whole human seminal plasma from the male partner is recommended for initial screening of suspect cases. Before skin testing, the male donor must be screened for viral hepatitis, syphilis, and HIV infection, and if there is evidence of infection, *in vivo* procedures should not be performed. Whole seminal plasma is prepared from a fresh specimen of ejaculate. Semen is allowed to liquefy at room temperature and centrifuged at 4°C to separate seminal plasma containing supernatant from spermatozoa, which is then filter sterilized.[149-151] The male donor is also tested to control for irritant responses. A positive response is defined as a wheal of 3 mm greater than or equal to that produced with saline with a flare and a concomitant negative response in the male donor. Typically, intracutaneous skin testing to whole seminal plasma has not been performed as a screening test in that it has been previously demonstrated to result in a nonspecific irritant response. Therefore screening for seminal plasma hypersensitivity should be limited to skin prick testing to whole seminal fluid. It should be emphasized that protein allergens contained in whole seminal plasma might not be present in sufficient concentrations to elicit a positive response. Thus a negative skin prick test response to whole seminal plasma does not exclude allergic sensitization. In this case skin test reagents with high diagnostic sensitivity should be obtained by means of gel filtration (Sephadex G-100) of whole seminal plasma to isolate allergen-rich fractions.[149-151]

Percutaneous or intracutaneous responses to relevant seminal plasma protein fractions have been detected in all reported cases of anaphylaxis. The presence of positive serologic specific IgE antibodies to these fractions and specific skin tests to the same fractions is highly predictive of a successful treatment outcome with seminal plasma protein desensitization.[160]

Treatment

Consideration must be given to the psychological effect of this condition on the patient, her spouse, and the future of their marital relationship. Couples should be informed that successful pregnancies have been achieved after artificial insemination with sperm washed free of seminal plasma.[159] Once the diagnosis is suspected, the patient must be advised to avoid coital exposure to seminal fluid. This can be achieved by means of either temporary cessation of intercourse or with the correct use of latex condoms. Coitus interruptus is often not successful because of potential leakage of seminal fluid during intercourse, which can result in a reaction and is therefore discouraged. Condoms made from lambskin or a plastic polymer can be substituted in the latex-sensitive patient. If anaphylaxis is caused by seminal transfer of exogenous

allergens, the male partner should avoid the causative food or drug before engaging in sexual intercourse.[151,152] It is essential that patients and spouses be trained in the emergency use of subcutaneous epinephrine. Although there are reports of successful use of precoital treatment with antihistamines or intravaginal cromolyn sodium, these options have generally been ineffective in the prevention of severe anaphylaxis.[160]

There are couples for whom abstinence, regular use of condoms, or artificial insemination to achieve pregnancy are unacceptable options. In such situations immunotherapy with seminal plasma fractions of the male partner should be considered. This procedure should only be performed in specialized centers and under the supervision of experienced physicians. Several (usually 4-7) fraction pools that correspond to different absorption peaks are collected by means of elution of whole seminal plasma over a Sephadex G-100 column.[148-151,161] Fraction pools are concentrated, quantitated for protein, and filter sterilized. *In vivo* allergenicity is evaluated by means of end point intracutaneous threshold testing. Because of its known immunosuppressive properties, the first fraction pool representing the initial absorption peak and containing high-molecular-weight proteins should not be used.[151] After obtaining informed consent, subcutaneous injections of allergenic fractions are administered by using a rapid immunotherapy program beginning with a concentration that is at least 2 log dilutions higher than the end point threshold concentration. Because systemic reactions can occur during immunotherapy, emergency equipment necessary for treating anaphylaxis must be available. Injections are continued every 15 to 20 minutes until the highest available protein concentration is achieved for each allergenic fraction. Decreased or absent skin reactivity to treatment fractions and disappearance of serum specific IgE observed after immunotherapy has indicated that desensitization can be accomplished at the conclusion of the immunotherapy protocol. In highly sensitive patients injections might only be advanced over a period of weeks to months. An intravaginal instillation of fresh ejaculate should be used to confirm the efficacy of treatment. If a challenge is well tolerated, unprotected coitus can then be safely initiated. Intercourse must be continued on a regular schedule (2-3 times per week). Prolonged abstinence has resulted in loss of tolerance and recurrence of anaphylactic episodes.[149,151,155,161] If abstinence periods can be predicted, subcutaneous injections of relevant allergens might be resumed to prevent loss of tolerance.

Successful intravaginal graded challenges have been reported in women given diagnoses of human seminal plasma–induced anaphylaxis confirmed by means of skin prick test reactivity to whole seminal plasma.[162-167] Increasing 10-fold concentrations (1;10,000 to neat) of whole seminal plasma are deposited intravaginally at 20-minute intervals and followed by a frequent schedule of unprotected sexual intercourse. No procedure-related systemic reactions have been reported to date. This approach has been successful in preventing subsequent anaphylactic episodes. As with parenteral desensitization protocols, frequent intercourse (2-3 times per week) is required to maintain the desensitized state. One case reported that abstinence for as short as 5 days resulted in recurrence of a postcoital reaction. The efficacy of intravaginal graded challenge is based entirely on single anecdotal reports. Because decreased percutaneous reactivity to seminal plasma has not been demonstrated, it is unknown whether the intravaginal approach represents true desensitization. Moreover, the duration of the protective effect is unknown. Graded intravaginal challenges have been less effective in women with localized seminal plasma–induced hypersensitivity reactions.[168]

Finally, it is very important to inform women with this problem that although seminal plasma hypersensitivity can cause significant stress on interpersonal relationships, it has no effect on their ability to get pregnant because it has not been associated with infertility.[166,168]

EXERCISE-INDUCED ANAPHYLAXIS

Summary Statements

45. Exercise-induced anaphylaxis is a form of physical allergy. Premonitory symptoms can include diffuse warmth, itching, and erythema. Urticaria generally ensues, with progression to confluence and often angioedema. Episodes can progress to include gastrointestinal symptoms, laryngeal edema, and/or vascular collapse. **B**
46. Factors that have been associated with exercise-induced anaphylaxis include medications (eg, aspirin or other nonsteroidal anti-inflammatory drugs) or food ingestion before and after exercise. **C**
47. Patients with exercise-induced anaphylaxis might have a higher incidence of personal and/or family history of atopy. **C**
48. Medications used prophylactically are not useful in preventing exercise-induced anaphylaxis. **C**
49. If exercise-induced anaphylactic episodes have been associated with the ingestion of food, exercise should be avoided in the immediate postprandial period. **C**
50. Patients with exercise-induced anaphylaxis should carry epinephrine and should wear and/or carry Medic Alert identification denoting their condition. They should have a companion with them when exercising. This companion should be versed in the use of an EpiPen. **D**

Exercise-induced anaphylaxis is a form of physical allergy. Initial symptoms typically include diffuse warmth, pruritus, erythema, and urticaria, with progression to angioedema, gastrointestinal symptoms, fatigue, laryngeal edema, and/or vascular collapse.[169] Symptoms can persist for 30 minutes to hours. Transient loss of consciousness occurs in about a third of patients because of vascular collapse, whereas symptoms of upper respiratory tract obstruction occur in almost two thirds of patients.

Jogging is a common activity precipitating attacks, but brisk walking, bicycling, racquet sports, skiing, and aerobic exercise might also be associated with such anaphylactic reactions.[170-172] In some patients exercise-induced anaphylaxis will only occur after ingestion of a specific food or medication, such as aspirin or other nonsteroidal anti-inflammatory agents. Ingestion of these medications before exercise has been reported by 13% of affected individuals,[173] and their elimination might enable the patient to tolerate exercise. Exercise-induced anaphylaxis in the postprandial state, without identification of a specific food, occurred in 54% of the respondents in the same survey. Exercise-induced anaphylaxis has also been reported when a certain food is ingested after, as well as before, exercise (see food allergy parameter). In some patients specific foods have been shown to trigger these reactions. Elimination of these foods might allow the patient to exercise without anaphylaxis development.[113,173-176] These patients might ingest these foods without anaphylaxis development if they do not exercise for 4 to 6 hours after eating them. Provocation of exercise-induced anaphylaxis with a latency period after food consumption of 24 hours has been reported.[113] For this reason, it is prudent to individualize this management recommendation, particularly for individuals with postparandial (nonfood specific) exercise-induced anaphylaxis. It should also be clear that these foods might be ingested in the absence of exercise without difficulty. Thus both exercise and food ingestion are necessary to produce the reaction. Individuals who have exercise-induced anaphylaxis might have a higher incidence of a personal and/or family history of atopy.[170]

Exercise-induced anaphylaxis should be distinguished from other exercise-associated medical conditions. Arrhythmias or other isolated cardiovascular events related to exercise can be first seen with vascular collapse but are not associated with pruritus, erythema, urticaria-angioedema, or upper respiratory obstruction. Patients who have exercise-induced anaphylaxis usually have wheezing in association with other symptoms of anaphylaxis, whereas patients who have exercise-induced bronchospasm have symptoms referable only to the lower respiratory tract.

Cholinergic urticaria is a physical allergy characterized by the development of punctate (1-3 mm diameter), intensely pruritic wheals with erythematous flaring after an increase in core body temperature or stress. A minority of individuals with exercise-induced anaphylaxis have cutaneous lesions consistent with cholinergic urticaria. Classic cholinergic urticaria elicited by means of exercise, as noted above, is characteristically associated with an increase in the core body temperature without vascular collapse. However, in 2 of 16 patients who did not have punctate urticaria with increase of core body temperature, a syndrome resembling exercise-induced anaphylaxis was seen with punctate urticaria progressing to collapse.[171] Unlike cholinergic urticaria, simply increasing the core body temperature does not necessarily produce symptoms of exercise-induced anaphylaxis. In addition, these syndromes might rarely appear concurrently.

A detailed history of symptoms associated with the first episode, as well as previous attacks, should be obtained. The history should include details concerning activities and ingestants that might precipitate an episode of anaphylaxis. Particular attention should be given to the antecedent use of aspirin or other nonsteroidal anti-inflammatory agents, as well as any seasonality to the attacks.

Prophylactic use of H_1 and H_2 antihistamines has generally not been effective in preventing exercise-induced anaphylaxis.[172] This is not without controversy, however, because reports have demonstrated in selected patients that antihistamine prophylaxis might help reduce the frequency and/or intensity of attacks.[177,178]

Early recognition of the prodromal manifestations of exercise-induced anaphylaxis is extremely important, with discontinuation of exercise at the earliest symptom. Modification of the exercise program by means of reduction in intensity or duration might be helpful in reducing episodes of exercise-induced anaphylaxis. Avoidance of exercise for 4 to 6 hours after eating is important in those individuals with documented exercise-induced anaphylaxis after food ingestion.

The emergency management of exercise-induced anaphylaxis is the same as that of anaphylaxis of other causes. The early administration of epinephrine is essential. Intravenous volume replacement, adequate oxygenation, and vigilance for upper airway compromise, with possible endotracheal intubation or tracheostomy, might also be required. H_1 blocking agents might be helpful but should not be relied on to abort the attack.

Affected individuals should discontinue exercise at the earliest symptom consistent with exercise-induced anaphylaxis, usually pruritus and cutaneous warmth or erythema (flushing). Such individuals should be accompanied during exercise by a companion aware of their condition and capable of providing emergency assistance. Patients with exercise-induced anaphylaxis should have injectable epinephrine available at all times of exercise for self-administration in the event of symptoms. Any patient who has a history consistent with food-dependent exercise-induced anaphylaxis should be told not to exercise for 4 to 6 hours after eating. There is controversy as to whether all patients should similarly be told not to exercise postprandially, and the decision to do so in such instances remains a clinical decision for the physician.

IDIOPATHIC ANAPHYLAXIS

Summary Statements

51. The symptoms of idiopathic anaphylaxis are identical to those of episodes related to known causes. **C**
52. Patients with idiopathic anaphylaxis should receive an intensive evaluation, including a meticulous history to rule out a definite cause of the events. **C**

53. There might be a need for specific laboratory studies to exclude systemic disorders, such as systemic mastocytosis. This might include a serum tryptase measurement when the patient is asymptomatic, measurement of the ratio of β-tryptase to total tryptase during an event, and selective allergy skin testing. **C**

In spite of efforts to define the pathogenesis of idiopathic anaphylaxis, we still do not know why patients experience these attacks. However, it is known that some might exhibit activated T cells shortly after episodes.[179]

The diagnosis of idiopathic anaphylaxis must be considered in those cases of anaphylaxis for which neither a causative allergen nor an inciting physical factor can be identified. Episodes can occur in both adults and children.[180-184]

The presenting manifestations of idiopathic anaphylaxis are identical to those of any form of anaphylaxis.[2] The vast majority of cases occur in adults, but there have been reports of episodes in children as well. Fatalities are rare but have occurred.[185]

The diagnosis of idiopathic anaphylaxis is a diagnosis of exclusion. Patients with idiopathic anaphylaxis should receive intensive evaluation, including a careful history with analysis of the events surrounding the development of the episodes. Clinical evaluation might indicate the need for specific laboratory studies, which might help to exclude an underlying systemic disorder, such as systemic mastocytosis. In addition, selective skin testing to foods (and if indicated to fresh food extracts) might be helpful.[103]

Because systemic mastocytosis can present as anaphylaxis of unknown cause, it is important to rule out this condition. The definitive test in this condition is a bone marrow biopsy, but serum tryptase levels can be helpful. In systemic mastocytosis, the baseline level (level obtained during an asymptomatic period) of total tryptase can be increased, whereas this is not the case in idiopathic anaphylaxis. In addition, the total β-tryptase to total tryptase ratio in systemic mastocytosis is usually greater than 20, whereas it is 10 or less in idiopathic anaphylaxis.[186]

The treatment of the acute episode is the same as the treatment for any other form of anaphylaxis. Various protocols have been published to prevent recurrent episodes. These protocols have recommended the administration of H_1 and H_2 antagonists, β-agonists, antileukotrienes, and corticosteroids. All of these have proved successful in individual cases. The decision to institute preventive therapy is under the aegis of the treating physician, and the decision to use a preventive protocol and the medications used should be based on the frequency and severity of recurrent episodes. Patients should of course be supplied a kit for the self-injection of epinephrine and should be instructed in its use. They should also have Medic Alert identification because syncope can occur during these events. Fortunately, the symptoms of most patients improve with time, and many undergo complete remission.[59,187,188]

ANAPHYLAXIS AND ALLERGEN IMMUNOTHERAPY VACCINES

Summary Statements

54. There is a small risk of near-fatal and fatal anaphylactic reactions to allergen immunotherapy injections. **C**

The rate of fatal anaphylaxis to allergen immunotherapy injections is approximately 1 in 2.5 million injections.[66,189-191] The rate of systemic reactions to allergen immunotherapy injections is approximately 0.5%.[192] Thus although severe systemic reactions to allergen immunotherapy are uncommon, physicians and patients should be prepared for possible systemic reactions after immunotherapy.

55. Patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to allergen immunotherapy injections **(C)**. Patients taking β adrenergic blocking agents are at higher risk for serious systemic reactions to allergen immunotherapy injections **(B)**.

Numerous studies suggest that patients with asthma, particularly poorly controlled asthma, are at higher risk for serious systemic reactions to allergen immunotherapy injections.[66,189,190,192-195] However, allergic asthma is an important clinical indication for allergen immunotherapy. Caution is advised when administering allergen immunotherapy vaccine if asthma is severe or poorly controlled. Many practitioners measure the peak expiratory flow rate before administering the allergen vaccine.

Patients receiving β-adrenergic blocking agents are at increased risk for more serious anaphylaxis.[66,196] Thus β-adrenergic blockade is a relative contraindication for allergen immunotherapy. The benefits of allergen immunotherapy might outweigh the risk of anaphylaxis to the allergen vaccine for patients with hypersensitivity to stinging insects.

56. Allergen immunotherapy vaccines should be administered only by health care professionals trained in the recognition and treatment of anaphylaxis, only in health care facilities with the proper equipment for the treatment of anaphylaxis, and in clinics with policies and procedures that minimize the risk of anaphylaxis. **D**

Allergen immunotherapy vaccines should be administered only by health care professionals trained in the recognition and treatment of anaphylaxis. Allergen immunotherapy should be administered only in health care facilities with the proper equipment for the treatment of anaphylaxis. Such equipment includes epinephrine, oxygen, antihistamines, corticosteroids, vasopressors, oral airway, and equipment for the administration of intravenous fluids and medications.

Allergen immunotherapy should be administered in clinics with policies and procedures that minimize the risk of anaphylaxis. These policies and procedures should reduce the risk of error, ensure proper

training of personnel, and facilitate treatment of anaphylaxis (practice parameters).

Most systemic reactions occur within 20 or 30 minutes after allergen vaccine administration, although late reactions do occur.[193,197] To better recognize and treat anaphylactic reactions, patients should wait in clinic for 20 or 30 minutes after receiving an allergen immunotherapy injection. In addition, patients who are at increased risk of systemic reactions, particularly if they previously have had a systemic reaction more than 30 minutes after an injection, might need to carry injectable epinephrine.[198] These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given. Such patients might also need to remain in the physician's office more than 30 minutes after an injection.

ANAPHYLAXIS TO DRUGS

Summary Statements

57. In most cases low-molecular-weight medications induce an IgE-mediated reaction only after combining with a carrier protein to produce a complete multivalent antigen. **B** A few drugs might elicit IgE-mediated reactions without first combining with a carrier protein.
58. Penicillin is the most common cause of drug-induced anaphylaxis. **C**
59. Penicillin spontaneously degrades to major and minor antigenic determinants, and skin testing with reagents on the basis of these determinants yields negative results in about 90% of patients with a history of penicillin allergy. **B**
60. The negative predictive value of penicillin skin testing (for immediate-type reactions) is between 97% and 99% (depending on the reagents used), and the positive predictive value is at least 50%. **B**
61. The extent of allergic cross-reactivity between penicillin and cephalosporins is unknown but appears to be low. A small percentage of patients proved to have penicillin allergy through penicillin skin testing react to cephalosporin challenges. **C**
62. Patients with a history of penicillin allergy who have negative penicillin skin test responses might safely receive cephalosporins. **B**
63. Patients with a history of penicillin allergy who have positive penicillin skin test responses might (1) receive an alternate (non–β-lactam) antibiotic, (2) receive a cephalosporin through graded challenge, or (3) receive a cephalosporin through rapid desensitization. **F**
64. Aztreonam does not cross-react with other β-lactams except ceftazidime, with which it shares a common R-group side chain. **B**
65. Carbapenems should be considered cross-reactive with penicillin. **C**
66. Diagnosis of IgE-mediated reactions to non–β-lactam antibiotics is limited by a lack of knowledge of the relevant allergenic determinants and/or metabolites. **C**
67. Aspirin and nonsteroidal anti-inflammatory drugs are the second most common cause of drug-induced anaphylactic reactions. **C**
68. Anaphylactic reactions to aspirin and nonsteroidal anti-inflammatory drugs appear to be medication specific and do not cross-react with structurally unrelated aspirin or other nonsteroidal anti-inflammatory drugs. **D**
69. Anaphylactic reactions to aspirin and nonsteroidal anti-inflammatory drugs appear to be medication specific and do not cross-react with structurally unrelated aspirin or other nonsteroidal anti-inflammatory drugs. **D**

Introduction

Medications are a common cause of anaphylaxis. Drug-induced anaphylactic reactions are due to the development of drug-specific IgE antibodies during a preceding period of sensitization, typically during a previous course with the same or cross-reacting compound. The relatively low molecular weight of most drugs prevents them acting as complete antigens and inducing an immune response. In most cases medications must first combine with larger carrier molecules (eg, normal tissue or serum proteins) to form an immunogenic multivalent antigen. A few drugs might elicit IgE-mediated reactions without first combining with a carrier protein. Furthermore, most drugs are not chemically reactive in their native state. They need to undergo degradation or metabolism to produce reactive intermediates, which then covalently bind to host proteins and might lead to an allergenic response with the production of IgE antibodies. In some cases the allergenic determinants against which specific IgE is directed are known, such as with penicillin, and immediate type skin testing can be performed to aid in diagnosis. In most situations the allergenic determinants are unknown, and the diagnosis can only be made clinically.

Some drugs are also capable of causing anaphylactoid reactions, which are due to direct nonimmunologic mast cell degranulation and do not require a preceding sensitizing period. Anaphylactoid reactions typically occur on initial exposure to a given drug and do not require a period of sensitization. Some medications are capable of causing both anaphylactic and anaphylactoid reactions, and because of this, it might be difficult to determine the cause of a given reaction.

Antibiotics

Penicillins. Penicillin is the most common cause of drug-induced anaphylaxis.[199] Under physiologic conditions, penicillin spontaneously degrades to reactive intermediates, which are broadly categorized into major and minor antigenic determinants. Because the immunochem-

istry of penicillin is well characterized, validated skin testing reagents representing the various allergenic determinants have been developed. In large-scale studies about 90% of patients with a history of penicillin allergy have negative penicillin skin test responses.[200,201]

The positive predictive value of penicillin skin testing is 50% or greater.[201,202] Patients with positive penicillin skin test responses should receive an alternate antibiotic or undergo rapid desensitization if administration of penicillin is mandated. The negative predictive value of penicillin skin testing (for immediate-type reactions) is between 97% and 99%, depending on the skin test reagents used.[200,201,203] Patients with negative penicillin skin test responses might be safely treated with penicillin, and depending on the reagents used for skin testing, the therapeutic dose might be preceded by a test dose.

Penicillin skin testing is safe in that the risk of inducing serious reactions during properly performed penicillin skin testing is comparable with the risk of other types of skin testing.[204] Penicillin skin testing itself might sensitize a very small proportion of patients.[205] Skin testing with semisynthetic penicillins, such as ampicillin or amoxicillin, is not standardized, and its predictive value is unknown. Penicillin skin testing should not be performed on patients with histories of severe non–IgE-mediated allergic reactions to penicillin, such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Cephalosporins. Penicillins and cephalosporins share a common β-lactam ring, but the extent of allergic cross-reactivity between the 2 families appears to be relatively low. Recent studies demonstrated no serious allergic reactions in large groups of patients with a history of penicillin allergy who were treated with cephalosporins.[206,207] Patients in these retrospective studies, however, were given diagnoses of penicillin allergy on the basis of self-report. Patient history is known to be poor predictor of true penicillin allergy in that about 90% of patients with such a history turn out to have negative penicillin skin test responses and are able to tolerate penicillin.[200,201] A review of the published literature showed that among patients with a history of penicillin allergy who were proved to have positive penicillin skin test responses, only a small percentage of patients experienced an allergic reaction on being challenged with cephalosporins.[208] However, fatalities have occurred when patients are not skin tested for penicillin and given cephalosporins.[209] There are distant case reports of cephalosporin-induced anaphylactic reactions in patients with a history of penicillin allergy,[210,211] but these patients did not undergo penicillin skin testing, and early cephalosporins were also known to contain trace amounts of penicillin.

Patients with a history of penicillin allergy who have negative penicillin skin test responses might receive cephalosporins because they are at no higher risk of experiencing allergic reactions.[212] In patients with a history of penicillin allergy who have positive penicillin skin test responses, the physician has 3 options: (1) administration of an alternate non–β-lactam antibiotic; (2) administration of a cephalosporin through graded challenge; or (3) desensitization to the cephalosporin.[212]

Other β-lactam antibiotics. Monobactams (aztreonam) do not-cross react with penicillin or other β-lactams, aside from ceftazadime, with which it shares an identical R-group side chain.[213] Therefore patients allergic to penicillin and other β-lactams (except for ceftazidime) might safely receive aztreonam. Similarly, patients allergic to aztreonam might safely receive other β-lactams, except for ceftazidime.

Skin test studies indicate allergic cross-reactivity between carbapenems and penicillin.[214] Although clinical challenge studies in patients with penicillin allergy are lacking, carbapenems should be considered cross-reactive with penicillin.

Non–β-lactam antibiotics. Non–β-lactam antibiotics appear to be uncommon causes of anaphylactic reactions. Diagnosis of IgE-mediated allergy to these drugs is more difficult because of lack of knowledge (in most cases) of the relevant metabolites and allergenic determinants. Skin testing with the native antibiotic can yield some useful information because if a nonirritating concentration is used, a positive result suggests the presence of drug-specific IgE antibodies.[215] However, the positive predictive value of such testing is unknown, and the negative predictive value is even less certain. Therefore diagnosis of anaphylactic reactions to non–β-lactam antibiotics is primarily based on the patient's history.

Aspirin and nonsteroidal anti-inflammatory drugs. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2–specific inhibitors, have all been described to cause anaphylactic reactions. Aspirin and NSAIDs appear to be the second most common cause of drug-induced anaphylaxis (after penicillin).[2,216] Anaphylactic reactions are unrelated to other reactions caused by these drugs, such as respiratory reactions and exacerbations of chronic idiopathic urticaria.[217] Although the reactions are referred to as anaphylactic, in most cases efforts to detect drug-specific IgE antibodies (through skin testing or *in vitro* testing) have been unsuccessful. The reactions are assumed to be anaphylactic because generally patients are able to tolerate the drug for a period of time before a reaction ensues. Anaphylactic reactions to aspirin and NSAIDs appear to be medication specific in that allergic patients are able to tolerate other NSAIDs, but this is largely based on clinical experience rather than large-scale challenge studies.[217]

Cancer chemotherapeutic agents. Anaphylaxis to anticancer chemotherapy drugs is being encountered more frequently because use of these drugs has increased,[218] particularly the platinum-containing drugs, such as cisplatinum and carboplatinum. In some instances the solvent in which these drugs are formulated (Cremophor-L) might cause an anaphylactoid reaction.[219] Such anaphylactoid reactions to the drug product must be distinguished from anaphylaxis because of the drug. Skin testing to these agents is helpful in determining whether sensitivity exists and at what dose to proceed with sensitization if this is necessary.[220]

PREVENTION OF ANAPHYLAXIS

Summary Statements

70. Major risk factors related to anaphylaxis include, but are not limited to, prior history of such reactions, β-adrenergic blocker exposure, or atopic background. Atopic background might be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to medications.
71. Avoidance measures are successful if future exposure to drugs, foods, additives, or occupational allergens can be prevented. Avoidance of stinging and biting insects is also possible in many cases. Prevention of systemic reactions during allergen immunotherapy are dependent on the specific circumstances involved.
72. Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, access to medical care, and the patients' level of personal anxiety.
73. Pharmacologic prophylaxis should be used to prevent recurrent anaphylactoid reactions to radiographic contrast material, fluorescein, as well as to prevent idiopathic anaphylaxis. Prophylaxis with glucocorticosteroids and antihistamines markedly reduces the occurrence of subsequent reactions.
74. Allergen immunotherapy with the appropriate stinging insect venom should be recommended for patients with systemic sensitivity to stinging insects because this treatment is highly (90% to 98%) effective.
75. Desensitization to medications that are known to have caused anaphylaxis can be effective. In most cases the effect of desensitization is temporary, and if the medication is required some time in the future, the desensitization process must be repeated.
76. Patient education might be the most important preventive strategy. Patients should be carefully instructed about hidden allergens, cross-reactions to various allergens, unforeseen risks during medical procedures, and when and how to use self-administered epinephrine. Physicians should educate patients about the risks of future anaphylaxis, as well as the benefits of avoidance measures.

Radiographic contrast material (RCM) is used in more than 10 million radiologic examinations annually in the United States. The overall frequency of adverse reactions (including anaphylactoid and nonanaphylactoid reactions) is 5% to 8%, and life-threatening reactions occur with a frequency of less than 0.1% with conventional high-osmolality RCM.[221] Among the 5% to 8% of patients who experience an adverse reaction to conventional RCM, most have minor reactions that require no specific treatment.[222] Moderate reactions, such as severe vomiting, diffuse urticaria, or angioedema, that require therapy occur in about 1% of patients who receive RCM. Although studies quote a wide spectrum of mortality, a reasonable estimate is one in every 75,000 patients who receive RCM.[223] With the recent development of lower-osmolality RCM, it appears that the overall risk of anaphylactoid reactions is decreased to about one fifth that of conventional RCM.[224]

The prevalence of adverse reactions to RCM appears to be greatest in patients 20 to 50 years of age. When adverse reactions occur, however, they are usually most severe in elderly patients.

Patients who are at greatest risk for an anaphylactoid reaction to RCM are those who have experienced a previous anaphylactoid reaction to RCM. This risk can range from as low as 16% to as high as 44%.[225,226] Other patients at increased risk are asthmatic and atopic patients, as well as those receiving β-adrenergic blocking agents and patients with cardiovascular disease.[227-229] Anaphylactoid reactions have occurred when RCM is used for hysterosalpingograms, myelograms, and retrograde pyelograms.[225] With pretreatment and the use of lower-osmolarity agents, the risk can be reduced to approximately 1%.[230]

Anaphylactoid reactions to RCM are independent of the dosage or concentration of RCM. Clinically, these reactions are identical to immediate hypersensitivity IgE-mediated reactions (anaphylaxis) but do not appear to involve IgE or any other immunologic mechanism.[228]

In almost all instances, the infusion of RCM should be discontinued if symptoms begin. The treatment of anaphylactoid reactions to RCM is not different than the treatment of anaphylactic-anaphylactoid reactions in other settings.

If the patient has a history of a prior anaphylactoid reaction to RCM, pretreatment regimens for prevention of repeat anaphylactoid reactions have consisted of oral glucocorticosteroids, H_1 and H_2 antihistamines, and other medications, such as ephedrine. A regimen that has been commonly recommended in the past has been 50 mg of prednisone given orally 13, 7, and 1 hours before administration of RCM; 50 mg of diphenhydramine given orally or intramuscularly 1 hour before the administration of RCM; and 25 mg of ephedrine given orally 1 hour before RCM administration. However, modifications to this regimen have included lower doses of glucocorticosteroids, oral rather than intramuscular diphenhydramine or other H_1 antihistamines, additional use of H_2 antihistamines, and/or exclusion of ephedrine. If the patient has to undergo an emergency radiographic procedure, an emergency pretreatment protocol that has been used successfully consists of 200 mg of hydrocortisone administered intravenously immediately and every 4 hours until the RCM is administered, and 50 mg of diphenhydramine administered intramuscularly 1 hour before RCM.[229]

In a setting in which RCM is being administered, a differential diagnosis might include adult respiratory distress syndrome or noncardiogenic pulmonary edema. In at least 2 reports of failure of standard pretreatment regimens to prevent anaphylactoid reactions, the initial reactions were apparently caused by noncardiogenic

pulmonary edema rather than anaphylactoid reactions.[231,232] In addition, RCM can cause intravascular volume expansion and precipitate cardiogenic pulmonary edema in patients with ischemic cardiac disease.

Anaphylactoid reactions in patients receiving β-adrenergic blocking agents might require more intensive and prolonged treatment. Therefore a careful benefit-risk assessment should be made in patients receiving β-adrenergic blocking agents if there is a pre-existing increased risk of having an anaphylactoid reaction to RCM. There is no evidence that the inorganic iodine levels present in seafood are related to adverse events from RCM.

REFERENCES

1. Yocum MW, Butterfield J, Klein J, et al. Epidemiology of anaphylaxis in Olmstead County, a population-based study. J Allergy Clin Immunol 1999;104:452-6. **III**
2. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis: a review of 266 cases. Arch Intern Med 1995;155:1749-54. **III**
3. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a three year survey. Mayo Clin Proc 1994;69:16-23. **III**
4. Perez C, Tejedor MA, Hoz A, Puras V. Anaphylaxis: a descriptive study of 182 patients [abstract]. J Allergy Clin Immunol 1995;95:368. **III**
5. Coghlan-Johnston M, Lieberman P. Demographic and clinical characteristics of anaphylaxis [abstract]. J Allergy Clin Immunol 2001;107: S57. **III**
6. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000;106:762-6. IIa
7. Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiological observations. Prog Clin Biol Restriction 1989;297: 175. **III**
8. Ditto A, Harris K, Krasnick J, et al. Idiopathic anaphylaxis: a series of 335 cases. Ann Allergy Asthma Immunol 1996;77:285-91. **III**
9. Wiggins CA. Characteristics and etiology of 30 patients with anaphylaxis. Immun Allergy Pract 1991;13:313-6. **III**
10. Perez C, Tejdor M, de la Hoz B, et al. Anaphylaxis: a descriptive study of 182 patients [abstract]. J Allergy Clin Immunol 1995;95:368. **III**
11. Lieberman P. Unique clinical presentations of anaphylaxis. Immunol Allergy Clin North Am 2001;21:813-27. **III**
12. Cianferoni A, Novembre E, Lombardi E, et al. Clinical features of severe acute anaphylaxis in patients admitted to a university hospital: an 11 year retrospective review. J Allergy Clin Immunol 2001;107: S57. **III**
13. Dibs SD, Baker MD. Anaphylaxis in children: a 5 year experience. Pediatrics 1997;99:7. **III**
14. Alonso MAT, Dominguez JS, Sanchez-Hernandez JJ, Frances C, Caballer BH. Idiopathic anaphylaxis: a descriptive study of 81 patients in Spain. Ann Allergy Asthma Immunol 2001;88:1-6. **III**
15. Viner NA, Rhamy RK. Anaphylaxis manifested by hypotension alone. J Urol 1975;113:108. **III**
16. Soreide E, Harboe S. Severe anaphylactic reactions outside hospital: etiology, symptoms and treatment. Acta Anaesthesiol Scand 1988;32: 339-42. **III**
17. Tan B, Fox R, Lockey R, Good R. Imported fire ant anaphylaxis is associated with seizure—a case report [abstract]. J Allergy Clin Immunol 2000;105:S58. **III**
18. Valabhji J, Robinson S, Johnston D, et al. Unexplained loss of consciousness: systemic mastocytosis. J R Soc Med 2000;93:141-2. **III**
19. Brown SGA, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. Emerg Med J 2004;21:149-54. **III**
20. Sticherling M, Brasch J. Alcohol: intolerance syndromes, urticarial and anaphylactoid reactions. Clin Dermatol 1999;17:417-22. **III**
21. LeHane L. Update on histamine fish poisoning. Med J Aust 2000;173: 149-52. **III**
22. Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. Hematol Oncol Clin North Am 2000;14:641-57. **III**
23. Lin R, Schwartz L, Curry A, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. J Allergy Clin Immunol 2000;106:65-71. IIb
24. Schwartz LB, Yunginger JW, Miller J, et al. The time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. J Clin Invest 1989;83:1551-5. IIb
25. LaRoche D, Vergnaud M, Sillard B, et al. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. Anesthesiology 1991;75:945-9. IIb
26. Kaliner M, Dyer J, Merlin S, et al. Increased urine histamine and in contrast media reactions. Invest Radiol 1984;19:116. IIb
27. Yunginger JW, Nelson DR, Squillace DL, et al. Laboratory investigation of deaths due to anaphylaxis. J Forensic Sci 1991;36: 857-65. IIb
28. Randall D, Butts J, Halsey J. Elevated postmortem tryptase in the absence of anaphylaxis. J Forensic Sci 1995;40:208-11. IIb
29. Edston E, Gidlund E, Wickman M, et al. Increased mast cell tryptase in sudden infant death syndrome: anaphylaxis, hypoxia, or artifact? Clin Exp Allergy 1999;29:1648-54. **III**
30. Edston E, van Hag-Hamsten M. Beta-tryptase measurements postmortem in anaphylactic deaths in controls. Forensic Sci Int 1998;93: 135-42. IIb
31. Project Team of the Resuscitation Council (UK). Emergency medical treatment of anaphylactic reactions. J Accid Emerg Med 1999;16: 243-7. IIb
32. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol 2002;110:341-8. IIb
33. Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiologic observations. Proc Clin Biol Res 1989;297:175-82. IIb
34. Brazil E, MacNamara AF. Not so immediate hypersensitivity—the danger of biphasic allergic reactions. J Accid Emerg Med 1998;15: 252-3. **III**
35. Douglas DM, Sukenick E, Andrade WP, et al. Biphasic systemic anaphylaxis: an inpatient and outpatient study. J Allergy Clin Immunol 1994;93:977-85. IIb
36. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. J Allergy Clin Immunol 1986;78:76-83. IIb
37. Fisher M. Clinical observations on the pathophysiology and implications for treatment. In: Vincent JL, editor. Update in intensive care and emergency medicine. New York: Springer-Verlag; 1989. p. 309-16. IIb
38. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. Anaesth Intensive Care 1986; 14:17-21. **IV**
39. Board of Directors: American Academy of Allergy and Immunology. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. J Allergy Clin Immunol 1994; 93:811-2. **IV**
40. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy 1998;53(suppl):S1-S42. IIb
41. Cummins RO, Hazinski MR, Baskett PJF, et al, editors. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: an international consensus on science. American Heart Association in collaboration with the International Liaison Committee on Resuscitation (ILCOR). Part 8: advanced challenges in resuscitation. Section 3: special challenges in ECC. Anaphylaxis. Circulation 2000; 102(suppl I):I241–I243. IIb
42. AAAI Board of Directors. The use of epinephrine in the treatment of anaphylaxis. J Allergy Clin Immunol 1994;94:666-8. IIb
43. Raymondos K, Panning B, Leuwer M, et al. Absorption and hemodynamic effects of airway administration of adrenaline in patients with severe cardiac disease. Ann Intern Med 2000;132:800-3. IIb
44. AAAAI Board of Directors. Anaphylaxis in schools and other childcare settings. J Allergy Clin Immunol 1998;102:173-6. **IV**
45. Cydulka R, Davison R, Grammer L, Parker M, Mathews J. The use of epinephrine in the treatment of older adult asthmatics. Ann Emerg Med 1988;17:322-6. IIb
46. Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998; 101:33-7. IIb
47. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001;108:871-3. IIb

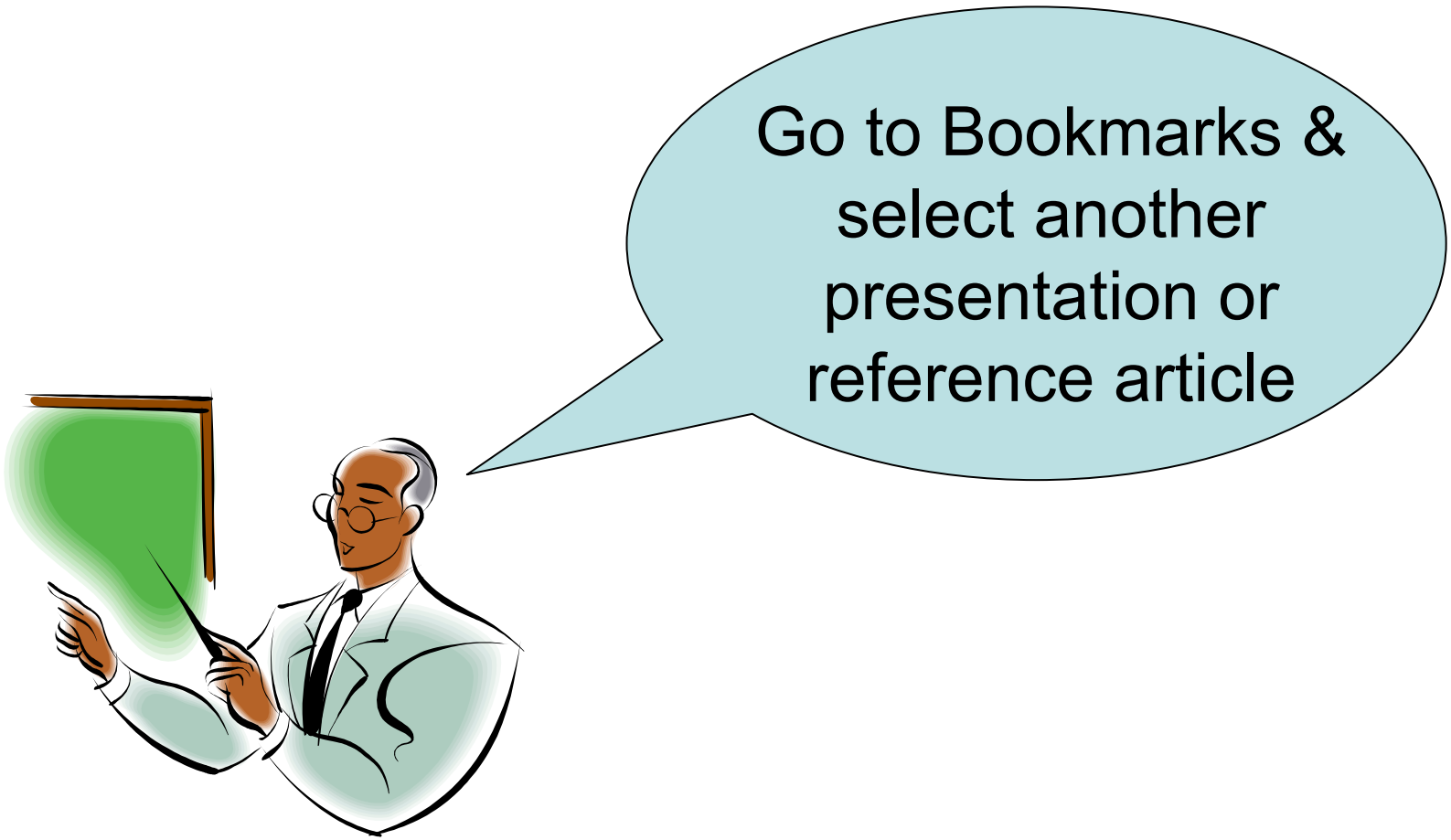
48. Cummins RO, Hazinski MR, Baskett PJF, et al, editors. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: an international consensus on science. American Heart Association in collaboration with the International Liaison Committee on Resuscitation (ILCOR). Part 10: pediatric advanced life support. Circulation 2000;102(suppl I):I291–I342. **IIb**
49. Vidovich RR, Heiselman DE, Hudock D. Treatment of urokinase-related anaphylactoid reaction with intravenous famotidine. Ann Pharmacother 1992;26:782-3. IIb
50. Kambam J, Merrill WH, Smith BE. Histamine receptor blocker in the treatment of protamine related anaphylactoid reactions: two case reports. Can J Anaesth 1989;36:463-5. IIb
51. Mayumi H, Kimura S, Asano M, et al. Intravenous cimetidine as an effective treatment for systemic anaphylaxis and acute allergic skin reactions. Ann Allergy 1987;58:447-50. IIb
52. DeSoto H, Turk M. Cimetidine in anaphylactic shock refractory to standard therapy. Anesth Analg 1989;69:264-5. IIb
53. Yarbrough JA, Moffitt JE, Brown DA, et al. Cimetidine in the treatment of refractory anaphylaxis. Ann Allergy 1989;63:235-8. IIb
54. Runge JW, Martinez JC, Caravati EM, et al. Histamine antagonists in the treatment of acute allergic reactions. Ann Emerg Med 1992;21: 237-42. Ib
55. Lin RY, Curry A, Pesola G, et al. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. Ann Emerg Med 2000;36:462-8. Ib
56. Brown AF. Therapeutic controversies in the management of acute anaphylaxis. J Accid Emerg Med 1998;15:89-95. IIb
57. Worobec AS, Metcalfe DD. Systemic anaphylaxis. In: Lichtenstein LM, Fauci AS, editors. Current therapy in allergy, immunology, and rheumatology. 5th ed. St Louis: Mosby-Year Book; 1996. p. 170-7. IIb
58. Kiowski W, Frei A. Bolus injection of cimetidine and hypotension in patients in the intensive care unit. Incidence and mechanisms. Arch Intern Med 1987;147:153-6. IIb
59. Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Adkinson NF Jr, Yunginger JW, Busse WW, et al, editors. Middleton's allergy: principles and practice. 6th ed. St Louis: Mosby-Year Book; 2003. p. 1497-522. IIb
60. Jacobs RL, Rake GW, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981;68:125-7. **III**
61. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. Ann Allergy 1981;47:35-7. **III**
62. Awai LW, Mekori YA. Insect sting anaphylaxis and beta-adrenergic blockade: a relative contraindication. Ann Allergy 1984;53:48-9. **III**
63. Laxenaire MC, Torrens J Moneret-Vautrin DA. Choc anaphylactoide mortel chez un malade traite par beta bloquants. Ann Fr Anesth Reanim 1984;3:453-5. IIb
64. Benitah E, Nataf P, Herman D. Accidents anaphylactiques chez des patients traites par beta-bloquants. Therapie 1986;41:139-42. IIb
65. Cornaille G, Leynadier F, Modiano, Dry J. Gravite du choc anaphylactique chez les maladies traites par beta-bloquers. Presse Med 1985;14: 790-1. IIb
66. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. J Allergy Clin Immunol 1987;79: 660-77. **III**
67. Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. CMAJ 1987;136:929-32. IIb
68. Berkelman RL, Finton RJ, Elsen WR. Beta adrenergic antagonists and fatal anaphylactic reactions to oral penicillin. Ann Intern Med 1986; 104:134. III
69. Capellier G, Boillot A, Cordier A, et al. Choc anaphylactique chez les malades sous betabloquers. Presse Med 1989;18:181. III
70. Madowitz JS, Scheweiger MJ. Severe anaphylactoid reaction to radiographic contrast media. JAMA 1979;241:2813-5. **III**
71. Hamilton G. Severe adverse reactions to urography in patients taking beta-adrenergic blocking agents. CMAJ 1985;133:122-6. **III**
72. Zaloga GP, Delacey W, Holmboe E, et al. Glucagon reversal of hypotension in a case of anaphylactoid shock. Ann Intern Med 1986; 105:65-6. **III**
73. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 1988;81:1-3. **III**
74. Lang DM. Anaphylactoid and anaphylactic reactions: hazards of beta-blockers. Drug Saf 1995;12:299-304. **III**
75. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk for anaphylactoid reaction from radiographic contrast media associated with both beta blocker exposure and cardiovascular disorders. Arch Intern Med 1993;153:2033-40. IIb
76. Shereff RH, Harwell W, Lieberman P, et al. Effect of beta-adrenergic stimulation and blockade on immediate hypersensitivity skin test reactions. J Allergy Clin Immunol 1973;52:328-33. **III**
77. Nisam MR, Zbinden A, Chesrown S, et al. Distribution and pharmacological release of histamine in canine lung in vivo. J Appl Physiol 1978;44:455-63. **III**
78. Matsumura Y, Tan EM, Vaughn JH. Hypersensitivity to histamine and systemic anaphylaxis in mice with pharmacologic beta adrenergic blockade: protection by nucleotides. J Allergy Clin Immunol 1976;58: 387-94. **III**
79. Hiatt WR, Wolfel EE, Stoll S, et al. Beta-2 adrenergic blockade evaluated with epinephrine after placebo, atenolol, and nadolol. Clin Pharmacol Ther 1985;37:2-6. **III**
80. Motulsky HJ, Insel PA. Adrenergic receptors in man. Direct identification, physiologic regulations, and clinical alterations. N Engl J Med 1982;307:18-29. **III**
81. American Academy of Allergy and Immunology. β-Adrenergic blockers, immunotherapy, and skin testing. J Allergy Clin Immunol 1989;84: 129-30. **IV**
82. Reports of deaths with allergenic extracts. FDA drug bulletin. Washington (DC): US Food and Drug Administration; 1988. p. 30-1. **III**
83. Psaty BM, Koepsell TD, Wagner EH, Loogerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of β-blockers. JAMA 1990;263:1653-7. **III**
84. Cesario D, Fonarow. Beta blocker therapy for congestive heart failure: the standard of care. Rev Cardiovasc Med 2002;3:14-21. **III**
85. Tenbrook J, Wolf M, Hoffman S, et al. Should beta blockers be given to patients with heart disease and peanut-induced anaphylaxis. J Allergy Clin Immunol 2004;114:127-30. **III**
86. Vander Zanden J, Valuck R, Bunch C, Perlman J, Anderson C, Wortman G. Systemic adverse effects of ophthalmic beta blockers. Ann Pharmacother 2001;35:1633-7. **III**
87. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta adrenergic blockers or with asthma. Ann Intern Med 1991;115:270-6. **III**
88. Kemp SF. Anaphylaxis: current concepts in pathophysiology, diagnosis, and management. Immunol Allergy Clin North Am 2001;21: 611-34. IIb
89. Pollack CV. Utility of glucagon in the emergency department. J Emerg Med 1993;11:195-205. **IV**
90. Sherman MS, Lazar EJ, Eichacker P. A bronchodilator action of glucagon. J Allergy Clin Immunol 1988;81:908-11. Ib
91. Fahmy NR. Hemodynamics, plasma histamine and catecholamine concentrations during an anaphylactoid reaction to morphine. Anesthesiology 1981;55:329-31. **IV**
92. van der Linden P-WG, Struyvenberg A, Kraaijenhagen RJ, et al. Anaphylactic shock after insect-sting challenge in 138 persons with a previous insect-sting reaction. Ann Intern Med 1993;118:161-8. IIb
93. Hermann K, Rittweger R, Ring J. Urinary excretion of angiotensin I, II, arginine vasopressin and oxytocin in patients with anaphylactoid reactions. Clin Exp Allergy 1992;22:845-53. IIb
94. Hanashiro PK, Weil MH. Anaphylactic shock in man: report of two cases with detailed hemodynamics and metabolic studies. Arch Intern Med 1967;119:129-40. IIb
95. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000;30:1144-50. **III**
96. Lindner KH, Dirks B, Strohmenger HU, et al. Randomized comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1997;349:535-7. Ib
97. Stiell IG, Hebert PC, Wells GA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomized controlled trial. Lancet 2001; 358:105-9. Ib
98. Wenzel V, Krismer AC, Arntz H, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105-13. Ib

99. Kill C, Wranze E, Wulf H. Successful treatment of severe anaphylactic shock with vasopressin. Int Arch Allergy Immunol 2004;134: 260-1. **IV**
100. Worster A. Vasopressin was not better than epinephrine for out-of-hospital cardiac arrest. ACP J Club 2004;141:2. **IV**
101. Bock SA. The incidence of severe adverse reactions to food in Colorado. J Allergy Clin Immunol 1992;90:683-5. **III**
102. Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in Northwest England. Clin Exp Allergy 1996;26:1364-70. **III**
103. Stricker WE, Anorve-Lopez E, Reed CD. Food skin testing in patients with idiopathic anaphylaxis. J Allergy Clin Immunol 1986;77:516-9. **III**
104. Bock SA. Anaphylaxis to coriander; a sleuthing story. J Allergy Clin Immunol 1993;91:1232-3. **III**
105. Yunginger JW, Sweeney KG, Sturner WQ, et al. Fatal food-induced anaphylaxis. JAMA 1988;260:1450-2. **III**
106. Yunginger JW. Lethal food allergy in children. N Engl J Med 1992;327: 421-2. **IV**
107. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal food anaphylaxis reactions in children. N Engl J Med 1992;327:380-4. **III**
108. Bock SA. Natural history of severe reactions to food in young children. J Pediatr 1985;107:676-80. IIb
109. Bernhisel-Broadbent J, Taylor S, Sampson HA. Cross-allergenicity in the legume botanical family in children with food hypersensitivity. J Allergy Clin Immunol 1989;84:701-9. IIa
110. Bock SA, Atkins FM. The natural history of peanut allergy. J Allergy Clin Immunol 1998;83:900-4. IIb
111. Bernhisel-Broadbent J, Scanlon SM, Sampson HA. Fish hypersensitivity I: in vitro and oral challenge results in fish-allergic patients. J Allergy Clin Immunol 1992;89:730-7. Ib
112. Sampson HA. Food allergy. JAMA 1997;278:1888-94. **IV**
113. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. J Allergy Clin Immunol 1979;63:433-4. **III**
114. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DYM. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992;90:256-62. Ib
115. Gern JE, Yang E, Evrard HM, Sampson HA. Allergic reactions to milk-contaminated ''nondairy'' products. N Engl J Med 1991;324:976-9. **III**
116. Jones RT, Squillace DL, Yunginger JW. Anaphylaxis in a milk-allergic child after ingestion of milk-contaminated kosher-pareve-labeled ''dairy-free'' dessert. Ann Allergy 1992;68:233-7. **III**
117. Toraason M, Sussman G, Biagini R, et al. Latex allergy in the workplace. Toxicol Sci 2000;58:5-14. **IV**
118. Ricci G, Gentili A, Di Lorenzo F, et al. Latex allergy in subjects who had undergone multiple surgical procedures for bladder exstrophy: relationship with clinical intervention and atopic disease. BJU Int 1999; 84:1058-63. III
119. Sussman GL, Beezhold DH, Kurup VP. Allergens and natural rubber proteins. J Allergy Clin Immunol 2002;110:S33-9. **IV**
120. Cogen FC, Beezhold DH. Hair glue anaphylaxis: a hidden latex allergy. Ann Allergy Asthma Immunol 2002;88:61-3. **III**
121. Fiocchi A, Restani P, Ballabio C, et al. Severe anaphylaxis induced by latex as a contaminant of plastic balls in play pits. J Allergy Clin Immunol 2001;108:298-300. **III**
122. AORN latex guideline. In: Standards, recommended practices and guidelines. Denver (CO): Association of Operating Room Nurses Inc; 1999. p. 93-108. **IV**
123. Alenius H, Kurup V, Kelly K, et al. Latex allergy: frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. J Lab Clin Med 1994;123: 712-20. IIb
124. Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Allergy principles and practice, Vol. II. 6th ed. St. Louis: Mosby; 2003. p. 1508. IV
125. Granady LC, Slater JE. History and diagnosis of latex allergy. Immunol Allergy Clin North Am 1995;15:21-30. **III**
126. Hamilton RG, Peterson EL, Ownby DR. Clinical and laboratory-based methods in the diagnosis of natural rubber latex allergy. J Allergy Clin Immunol 2002;110(suppl):S47-56. **IV**
127. Mertes PM, Laxenaire MC, Alla F. Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylactic and anphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003;99:521-3. **III**
128. Thong BY, Yeow-Chan. Anaphylaxis during surgical and interventional procedures. Ann Allergy Asthma Immunol 2004;92:619-28. **III**
129. Mertes PM, Laxeanire MC. Adverse reactions to neuromuscular blocking agents. Curr Allergy Asthma Rep 2004;4:7-16. **III**
130. Laurie SA, Khan DA, Gruchala RS, Peters G. Anaphylaxis to isosulfan blue. Ann Allergy Asthma Immunol 2002;88:64-6. **III**
131. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetized patients—four cases of chlorhexidine allergy (III). Act Anaesthesiol Scand 2001;45:1290-4. **III**
132. Lyew MA, Gamblin TC, Ayoub M. Systemic anaphylaxis associated with intramammary isosulfan blue injection used for sentinel node detections under general anesthesia. Anesthesiology 2000;93:1145-6. **III**
133. Peng Ch, Tan PH, Lin CH, Lin HY, Kuo CH, Chung HC. Fatal anaphylactoid shock associated with protamine for heparin reversal during anesthesia. Acta Anaesthesiol Sin 2000;38:97-102. **III**
134. Matthey P, Wang P, Finegan BA, Donnelly M. Rocuronium anaphylaxis and multiple neuromuscular blocking drug sensitivities. Can J Anaesth 2000;47:890-3. **III**
135. Heier T, Guttormsen AB. Anaphylactic reactions during induction of anaesthesia using rocuronium for muscle relaxation: a report including 3 cases. Acta Anaesthesiol Scand 2000;44:775-81. **III**
136. Soetens FM, Smolders FJ, Meeuwis HC, et al. Intradermal skin testing in the investigation of suspected anaphylactic reactions during anaesthesia—a retrospective survey. Acta Anaesthesiol Belg 2003;54: 59-63. IIb
137. Moscicki RA, Sockin SM, Corsello BF, et al. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. J Allergy Clin Immunol 1990;86:325-32. IIb
138. Ducart AR, Watremez C, Louagie YA, et al. Propofol-induced anaphylactoid reaction during anesthesia for cardiac surgery. J Cardiothorac Vasc Anesth 2000;14:200-1. **III**
139. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reaction. Drug anesthesia in Australia. Ann Fr Anesh Reanim 1993;12:97-104. IIb
140. Garcia JJ, Blanca M, Moreno F, et al. Determination of IgE antibodies to the benzylpenicilloyl determinant: a comparison of sensitivity and specificity of three radioallergosorbent tests methods. J Clin Lab Anal 1997;11:251-5. IIb
141. Kimmel SE, Sekeres MA, Berlin JA, Ellison N, DiSesa VJ, Srom BL. Risk factors for clinically important adverse events after protamine administration following cardiopulmonary bypass. J Am Coll Cardiol 1998;32:1916-22. IIb
142. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes incidence risk factors, mechanisms: a French multicenter prospective study. Ann Fr Anesh Reanim 1994; 13:301-10. IIb
143. Fisher MM, Doig GS. Prevention of anaphylactic reactions to anaesthetic drugs. Drug Saf 2004;27:393-410. **III**
144. deShazo R, Nelson HS. An approach to the patient with a history of local anesthetic hypersensitivity: experience with 90 patients. J Allergy Clin Immunol 1979;63:387-94. IIb
145. Specken JLH. Fen Merkwardig geval van allergi in de gynaedogie. Ned Tjidscr Verloskd Gynaecol 1958;58:314-8. **III**
146. Bernstein JA, Sugumaran R, Bernstein DI, Bernstein IL. Prevalence of human seminal plasma hypersensitivity among symptomatic women. Ann Allergy Asthma Immunol 1997;78:54-8. **III**
147. Presti ME, Druce HM. Hypersensitivity reactions to human seminal plasma. Ann Allergy 1978;85:103-7. **IV**
148. Levine BB, Siraganian RP, Schenkein I. Allergy to human seminal plasma. N Engl J Med 1973;288:894-6. **III**
149. Friedman SA, Bernstein IL, Enrione M, Marcus ZH. Successful long-term immunotherapy of human seminal plasma anaphylaxis. JAMA 1984;251:2684-7. IIb
150. Ohman JL, Malkiel S, Lewis S, Lorusso JR. Allergy to human seminal fluid: Characterization of the allergen and experience with immunotherapy. J Allergy Clin Immunol 1990;85:103-7. IIb
151. Bernstein IL, Englander BE, Gallagher JS, Nathan P, Marcus ZH. Localized and systemic hypersensitivity reactions to human seminal fluid. Ann Intern Med 1981;94:459-65. IIa
152. Green RL, Green MH. Post-coital urticaria in a penicillin-sensitive patient, possible seminal transfer of penicillin. JAMA 1985;254:531. **III**
153. Haddad ZH. Food allergens. Perspect Allergy 1978;1:2-3. **IV**

154. Holden TE, Sherline DM. Bestiality with sensitization and anaphylactic reaction. Obstet Gynecol 1973;42:138-40. **III**
155. Bernstein JA, Bernstein DI, Bernstein IL. Seminal plasma hypersensitivity. In: Amin S, Lahti A, Maibach HI, editors. Contact urticaria syndrome. Boca Raton (FL): CRC Press; 1997. p. 241-60. **IV**
156. Bernstein JA, Herd ZA, Bernstein DI, Korbee L, Bernstein IL. Evaluation and treatment of localized vaginal immunoglobulin E-mediated hypersensitivity to human seminal plasma. Obstet Gynecol 1993;82:667-73. IIb
157. Kint B, Degreef H, Dooms-Goosens. Combined allergy to human seminal plasma and latex: case report and review of the literature. Contact Dermatitis 1994;1:7-10. **III**
158. Mathias CGT, Frick OL, Caldwell TM, Yunginger JW, Malbach HI. Immediate hypersensitivity to seminal plasma and atopic dermatitis. Arch Dermatol 1980;116:209-12. **III**
159. Mumford DM, Haywood TJ, Daily LJ, et al. Female allergy to seminal plasma—a case report. Ann Allergy 1978;40:40-3. **III**
160. Bernstein JA, Perez A, Floyd R, Bernstein IL. Is burning semen syndrome a variant form of seminal plasma hypersensitivity? Obstet Gynecol 2003;101:93-102. IIa
161. Mittman RJ, Bernstein DI, Adler T, Korbee L, Gallagher JS, Bernstein IL. Selective desensitization to seminal plasma protein fractions after immunotherapy for post-coital anaphylaxis. J Allergy Clin Immunol 1990;86:954-60. IIb
162. Jones WR. Allergy to coitus. Aust N Z J Obstet Gynaecol 1991;31: 137-41. **II**
163. Goldenhersh MJ, Saxon A. Seminal fluid hypersensitivity: a new approach [abstract]. Ann Allergy 1989;2:256. **III**
164. Park JW, Ko SH, Kim CW, Bae SW, Hong CS. Seminal plasma anaphylaxis: successful pregnancy after intravaginal desensitization and immunodetection of allergens. Allergy 1999;54:990-3. **III**
165. Nusam D, Geva A, Kalderon I, Cohen S. Intravaginal desensitization to seminal fluid. Allergy 1999;54:765. **III**
166. De Cuyper C, Bogaerts Y, Vanderkerkhove F, Gunst J. Intravaginal desensitization and successful pregnancy in a woman with seminal fluid allergy. J Allergy Clin Immunol 1996;54:765. **III**
167. Matloff SM. Local intravaginal desensitization to seminal fluid. J Allergy Clin Immunol 1993;91:1230-1. **III**
168. Resnick DJ, Hatzis DC, Kanganis P, Liccardi FL, Lee-Wong M, Bernstein JA. The approach to conception for women with seminal plasma protein hypersensitivity. Am J Reprod Immunol 2004;52:42-4. **III**
169. Shadick MA, Liang MH, Partridge, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10 year follow-up study. J Allergy Clin Immunol 1999;104:123-7. IIb
170. Sheffer AL, Austen KF. Exercise-induced anaphylaxis. J Allergy Clin Immunol 1980;66:106. **III**
171. Sheffer AL, Soder NA, McFadden ER Jr, et al. Exercise-induced anaphylaxis: a serious form of physical allergy. J Allergy Clin Immunol 1983;71:311. IIb
172. Kaplan AP, Nathony S, Tawal AP, et al. Exercise-induced anaphylaxis as a manifestation of cholinergic urticaria. J Allergy Clin Immunol 1981;68:319. IIb
173. Lewis J, Lieberman P, Treadwell G, et al. Exercise-induced urticaria, angioedema, and anaphylactic episodes. J Allergy Clin Immunol 1981; 68:432. **III**
174. Novey HS, Fairshter RD, Salness K, et al. Postprandial induced exercise anaphylaxis. Evidence of an association with the complement system. J Allergy Clin Immunol 1983;71:498-504. **III**
175. Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiologic observations. Prog Clin Biol Restrict 1989;297:175. **III**
176. Dohl M, Suko M, Suglyama H, et al. Food dependent exercise-induced anaphylaxis: a study on 11 Japanese cases. J Allergy Clin Immunol 1991;87:34. IIb
177. Kidd JM III, Cohen SH, Sosman AJ, et al. Food-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol 1983;71:4-7. **III**
178. Briner WW, Bruno PJ. Case report: 30 year old female with exercise-induced anaphylaxis. Med Sci Sports Exerc 1991;23:991-4. **III**
179. Grammer L, Shaughnessy M, Harris K, Goolsby C. Lymphocyte subsets and activation markers in patients with acute episodes of idiopathic anaphylaxis. Ann Allergy Asthma Immunol 2000;85: 368-71. IIb
180. Bacal E, Patterson R, Zeiss CR. Evaluation of severe (anaphylactic) reactions. Clin Allergy 1978;8:295-304. **III**
181. Lieberman P, Taylor WW Jr. Recurrent idiopathic anaphylaxis. Arch Intern Med 1979;139:1032-4. **III**
182. Orfan NA, Stoloff RS, Harris KE, Patterson R. Idiopathic anaphylaxis: total experience with 225 patients. Allergy Proc 1992;13:35-43. **III**
183. Wiggins CA, Dykewicz MS, Patterson R. Idiopathic anaphylaxis: classification, evaluation, and treatment of 123 patients. J Allergy Clin Immunol 1988;82:849-55. **III**
184. Patterson R, Hogan M, Yarnold P, et al. Idiopathic anaphylaxis. Arch Intern Med 1995;155:869-71. **III**
185. Krasnick J, Patterson R, Meyers G. A fatality from idiopathic anaphylaxis. Ann Allergy Asthma Immunol 1996;76:376-9. **III**
186. Schwartz LB, Irani AM. Serum tryptase in the laboratory diagnosis of systemic mastocytosis. Hematol Oncol Clin North Am 2000;14: 641-57. **III**
187. Yocum M, Kahn D. Clinical cause of idiopathic anaphylaxis. Ann Allergy 1994;13:370-4. **III**
188. Tejedor A, Sastre DJ, Sanchez-Hernandez JJ, et al. Idiopathic anaphylaxis: a descriptive study of 81 patients in Spain. Ann Allergy Asthma Immunol 2002;88:313-8. **III**
189. Bernstein DI, Wanner M, Borish L, et al. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;113:1129-36. **III**
190. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87:47-55. **III**
191. Reid MJ, Lockey RF, Turkeltaub PC, Platts Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993;92:6-15. **III**
192. Matloff SM, Bailit IW, Parks P, et al. Systemic reactions to immunotherapy. Allergy Proc 1993;14:347-50. **IV**
193. Frew AJ. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. BMJ 1993;307:919-23. **IV**
194. Practice parameters: anaphylaxis and allergen immunotherapy extracts. Ann Allergy Asthma Immunol 2003;90:1-40. **IV**
195. Ragusa FV, Passalacqua G, Gambardella R, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 1997;7:151-4. **III**
196. Tabar AI, Garcia BE, Rodriguez A, Olaguibel JM, Muro MD, Quirce S. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. Allergy 1993;48:450-3. IIb
197. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta adrenergic blockers or with asthma. Ann Intern Med 1991;115:270-6. **III**
198. Greenberg MA, Kaufman CR, Gonzalez GE, Rosenblatt CD, Smith LJ, Summers RJ. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986;77: 865-70. **III**
199. Idsoe O, Guthe T, Willcox RR, DeWeck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull World Health Organ 1968;38:159-88. **III**
200. Gadde J, Spence M, Wheeler B, Adkinson NF. Clinical experience with penicillin skin testing in a large inner-city STD Clinic. JAMA 1993; 270:2456-63. **III**
201. Sogn DD, Evans R, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med 1992;152: 1025-32. IIa
202. Green GR, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. J Allergy Clin Immunol 1977; 60:339-45. IIb
203. Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. J Allergy Clin Immunol 1984;73:76-81. **III**
204. Valyasevi MA, VanDellen RG. Frequency of systematic reactions to penicillin skin tests. Ann Allergy Asthma Immunol 2000;85:363-5. **III**
205. Nugent FS, Quinn FM, McGrath CM, Hrncir DE, Boleman WT, Freeman TM. Determination of the incidence of sensitization after penicillin skin testing. Ann Allergy Asthma Immunol 2003;90:398-403. IIb

206. Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. J Allergy Clin Immunol 2004;113:1220-2. **III**
207. Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. J Clin Anesth 2001;13:561-4. **III**
208. Solensky R. Hypersensitivity reactions to beta-lactam antibiotics. Clin Rev Allergy Immunol 2003;24:201-19. **III**
209. Pumphrey RS, Davis S. Underreporting of antibiotic anaphylaxis may put patients at risk. Lancet 1999;353:1157. **III**
210. Scholand JF, Tennenbaum JI, Cerilli GJ. Anaphylaxis to cephalothin in a patient allergic to penicillin. JAMA 1968;206:130-2. **IV**
211. Rothschild PD, Doty DB. Cephalothin reaction after penicillin sensitization. JAMA 1966;196:372-3. **IV**
212. Bernstein IL, Gruchalla RS, Lee RE, Nicklas RA, Dykewicz MS. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy Asthma Immunol 1999;83:665-700. **IV**
213. Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson NF. Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. J Infect Dis 1984;149: 16-22. IIb
214. Saxon A, Adelman DC, Patel A, Hajdu R, Calandra GB. Imipenem cross-reactivity with penicillin in humans. J Allergy Clin Immunol 1988;82:213-7. IIa
215. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol 2003;112:629-30. IIb
216. Brown AFT, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. J Allergy Clin Immunol 2001; 108:861-6. **III**
217. Stevenson DD. Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am 2004;24:491-505. **IV**
218. Choi J, Hartnett P, Fulcher DA. Carboplatin desensitization. Ann Allergy Asthma Immunol 2004;93:137-41. **IV**
219. Moreno-Ancillo A, Dominguez-Noche C, Gil-Adrados AC, et al. Anaphylactoid reaction to carboplatin: successful ''desensitization''. Allergol Immunopathol (Madr) 2003;31:342-4. **IV**
220. Markham M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for presence or absence of carboplatin hypersensitivity. J Clin Oncol 2003;15:4611-4. **III**
221. Bush WH. Treatment of systemic reactions to contrast media. Urology 1990;35:145-50. **IV**
222. Shehadi WH, Toniolo G. Adverse reactions to contrast media. Radiology 1980;137:299-302. **III**
223. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media; report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990;175:621-8. **III**
224. Bettman MA. Ionic versus nonionic contrast agents for intravenous use: are all the answers in? Radiology 1990;175:616-8. **IV**
225. Lieberman P. Anaphylactoid reactions to radiocontrast material. In: Reisman R, Lieberman P, editors. Immunol Allergy Clin North Am 1992;12:649-70. **IV**
226. Bush WH, Swanson DP. Acute reactions to intravascular contrast media: types, risk factors, recognition, and specific treatment. Am J Roentgenol 1991;157:1153-61. **IV**
227. Enright T, Chua-Lim A, Duda E, Lim DT. The role of a documented allergic profile as a risk factor for radiographic contrast media reaction. Ann Allergy 1989;62:302-5. **IV**
228. Thrall JF. Adverse reactions to contrast media. In: Swanson DP, Chilton HM, Thrall JH, editors. Pharmaceutical in medical imaging. New York: Macmillan; 1990. **IV**
229. Greenberger PA, Halwig TM, Patterson R, et al. Emergency administration of a radiocontrast media in high risk patients. J Allergy Clin Immunol 1986;77:630. **III**
230. Greenberger P, Patterson R. Beneficial effects of lower osmolality contrast media in pretreated high risk patients. J Allergy Clin Immunol 1991;87:867-72. **III**
231. Borish L, Matloff SM, Findlay SR. Radiographic contrast media-induced noncardiogenic pulmonary edema: case report and review of the literature. J Allergy Clin Immunol 1984;74:104. **IV**
232. Madowitz J, Schweiger M. Severe anaphylactoid reactions to radiographic contrast media: occurrence despite premedication with diphenhydramine and prednisone. JAMA 1979;241:2813. **IV**

End of Selection



Name
Patient No.
DEPN

DATE: 22-SEP-04
DR. MONTGOMERY, J.

NATIONAL NAVAL MEDICAL CENTER
ALLERGY CLINIC BLDG#9 1ST FL
8901 WISCONSIN AV (PICK UP)
BETHESDA, MD 20889-5600

RX# 283420 CONTAINS 1:200 W/V 2,000 AU/ML 11,000 BAU/ML

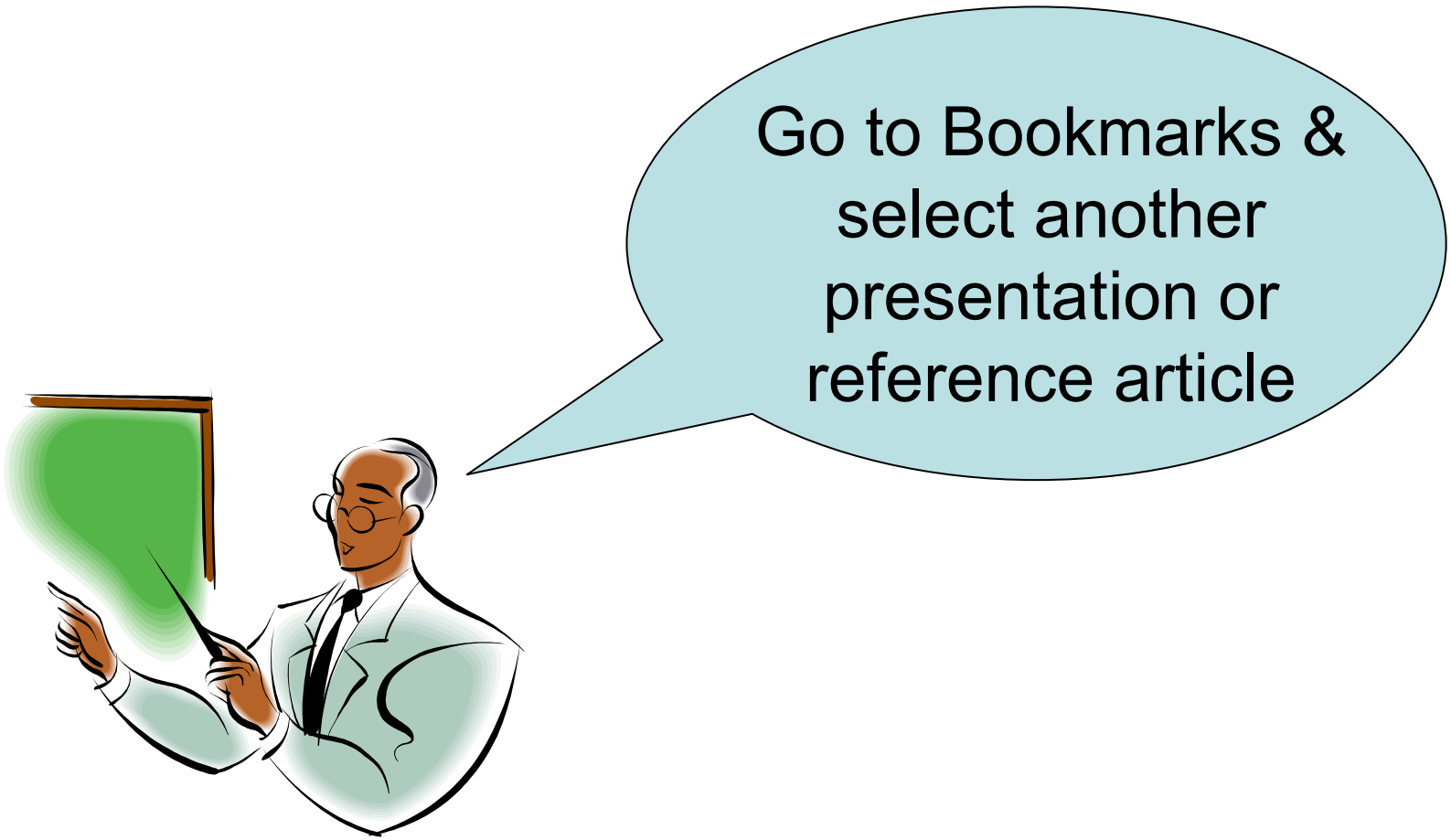
GRASSES	[BERMUDA (GREER)] 18824	10,000 BAU/ML	1.00ML
	[JOHNSON (GREER)] 23932	1:20 W/V	0.50ML
	[TIMOTHY (GREER)] 14434	100,000 BAU/ML	1.00ML
WEEDS	[LAMBS QTRS (GREER)] 11648	1:20 W/V	0.50ML
	[PLANTAIN, ENG (GREER)] 21045	1:10 W/V	0.50ML
	[RAGWEED MX (G/S) (GREER)] 12914	1:20 W/V	1.00ML
MITES	[MITES, MIX (GREER)] 13125	10,000 AU/ML	2.00ML
PHENOL SALINE			3.50ML
TOTAL FULL STRENGTH	1:200 W/V 2,000 AU/ML 11,000 BAU/ML	100%	10.00ML

NOTE:

LABEL AS: 1:2 MIL - 1:200 W/V VIAL# 1 - 5 22-SEP-04
LABEL AS: 1:200 - 1:200 W/V VIAL# 5 - 5 09-AUG-05

FILL RX FOR LAST LINE SHOWN: PREP MA INSP PKD DATE 9/12/05 RVW

End of Selection



Date _____

_____ CLINIC
Standard Operating Procedures

IMMUNOTHERAPY

1. **Purpose:** This operating instruction provides procedures to follow when administering immunotherapy.

2. **Responsibility:** All assigned Clinic personnel.

3. **References:**
   a. Allergen immunotherapy: a practice parameter. Ann Allergy Asthma Immunol. 2003 Jan;90(1 Suppl 1):1-40.
   b. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 2005 Mar;115(3 Suppl 2):S483-523

4. **General:**
   a. Immunotherapy (AIT) is initiated by the prescribing Allergist whose name and contact information will be readily available to all clinic staff. By design, the patient will arrive at the clinic with an allergen extract kit (allergy shot vials) that has originated from another facility/provider. The vials and accompanying documentation will be reviewed by the ____ Clinic's Physician-In-Charge assuring adherence to established standards to ensure appropriateness and safety before the patient receives his/her AIT. The prescribing Allergist is responsible for providing AIT extracts labled IAW Ref. (a), protocols for AIT administration and alteration in dosing in the event of an adverse reaction or missed doses, and for providing point of contact information. Allergen immunotherapy can be temporarily withheld without placing the patient at undue risk.
   b. An Allergy Treatment Record will be maintained on all patients receiving AIT in the Clinic. All AIT injections, reactions (immediate and delayed), and alterations in dosing will be recorded in this record. This record will contain the signed informed consent, Problem Summary List, AIT prescription, AIT administration instructions, AIT Adjustment protocol, name and contact information of the prescribing Allergist.
   c. Prior to beginning AIT, all patients or, in the case of a minor, the parent or legal guardian, will review/complete and sign all required forms including the informed consent, patient instruction sheet, and the problem list. In general, allergy shots will not be administered to patients on Beta blockers. Any patient on Beta blockers will have their shots withheld and will be referred to the Physician-In-Charge for further consultation with the prescribing Allergist.
   d. All persons under 18 years of age must be accompanied by a parent/legal guardian.

5. **Patient Instructions:**
   a. The Clinic's nurse/technician will instruct the patient about what is expected when AIT is begun.
   b. The patient will be informed that the allergen extract(s) will be maintained at the _____ Clinic. Patients will not be allowed to maintain their allergy extracts in their home.

c. The patient will be counseled concerning the possibility for adverse reactions and of the signs and symptoms preceding possible adverse reactions they may have after receiving their immunotherapy. The patient/guardian will sign the informed consent.

d. The dosage schedule in the patient's prescribed course of AIT will be discussed.

e. The nurse/technician must physically examine the injection site prior to the patient departing the clinic. The allotted time period for waiting after injection is a minimum of thirty minutes. If the use of the toilet is necessary before the end of the 30 minute wait, the nurse/technician must be informed, and only the handicapped (distress alarmed) toilet is to be used. Failure to remain in the patient waiting area for the prescribed time after injection may result in the termination of immunotherapy.

6. **Immunotherapy Procedures:**

a. Retrieve the patient's allergy record.

b. Retrieve the patient's extract from the refrigerated storage. Ensure that the extract pulled is for the right patient, that the vial content agrees with what is ordered on the Allergen Extract Prescription and is listed on the injection record.

c. Question the patient about any delayed local reaction or systemic symptoms. Make the appropriate adjustment in the dosage according to the provided protocol for that patient. If the patient states (s)he had a delayed systemic reaction, record this on the Immunotherapy Administration Form. An appointment with the Physician-In-Charge is necessary before proceeding with immunotherapy.

d. Check dosage advancement schedule for the amount of extract to be given. Document the dosage in the appropriate column on the Immunotherapy Administration Form. The nurse/technician administering the AIT will annotate the date and time of administration, the injection site (R or L), and initial the form.

e. Gently shake the vial before using. Draw up the dosage required using a tuberculin/1cc syringe and a 26 - 27 gage needle. Ensure that the pertinent information is checked; confirm this information with the patient.

(1) Right patient
(2) Right extract
(3) Right interval
(4) Right dosage
(5) Right method, route, and technique

f. Administer the allergy injection. Give the injection subcutaneously into the posterolateral surface of the middle third of the upper arm. Always pull back on the plunger before the allergy extract is administered; if blood returns, withdraw the needle and use the other arm. Avoid massaging the injection site to lessen unduly rapid absorption of the allergen.

g. Instruct the patient to wait 30 minutes in the clinic patient waiting area and to report any problems immediately.

h. Check the injection site(s) and annotate the appearance of the injection site(s) prior to the patient leaving the clinic.

i. Document all reactions in the patient's allergy record. Notify the Physician-In-Charge if there are recurrent local reactions preventing advancement of the patient’s AIT, any systemic reactions, or other problems affecting administration of immunotherapy.

j. Unless reactions dictate a change in dosage and/or the Physician-In-Charge (in consultation with the prescribing Allergist) annotates otherwise, the nurse/technician will always follow the

prescribed schedule on the Allergen Extract Prescription. Any questions will be directed to the Physician-In-Charge before administering the shot.

k. No patient will be permitted to administer their own injections.

7. Anaphylaxis Guidelines

a. In the event of signs or symptoms of anaphylaxis in a patient receiving AIT, the following guidelines will be initiated:

(1) Administer 0.3 cc of 1:1,000 **Epinephrine** IM (lateral thigh) if the patient complains of spreading hives, throat or chest tightness, cough, wheeze, vomiting, abdominal cramping, or lightheadedness (hypotension).

(2) **Alert** the medical provider (physician).

(3) Establish/maintain the **airway**.

(4) If difficulty in **breathing** occurs, administer oxygen 6-8 liters/min. via face mask.

(5) Monitor **blood pressure**, heart rate, O2 saturation (Pulse Oxymetry), and level of consciousness every 5 minutes until stable.

(6) If cardiopulmonary comprominse persists after 10-15 minutes have elaspsed since epinephrine was given, **repeat** 0.3 cc of 1:1,000 epinephrine (IM). Epinephrine may be repeated every 10-15 minutes if symptoms do not diminish or cease.

(7) If a second dose of epinephrine is required, notify the next echelon of care/EMS and expidite the **transfer** of the patient to a higher level of care.

b. This guideline is based upon the recognition of, but not limited to the following signs and/or symptoms:

(1) Generalized hives.

(2) Wheezing or chest tightness.

(3) Stridor.

(4) Erythema (redness of the face, trunk, and/or extremities).

(5) Edema (swelling of the face, tongue, and/or throat).

(6) Apprehension, weakness, or syncope (fainting).

(7) Nausea, vomiting, or abdominal cramping.

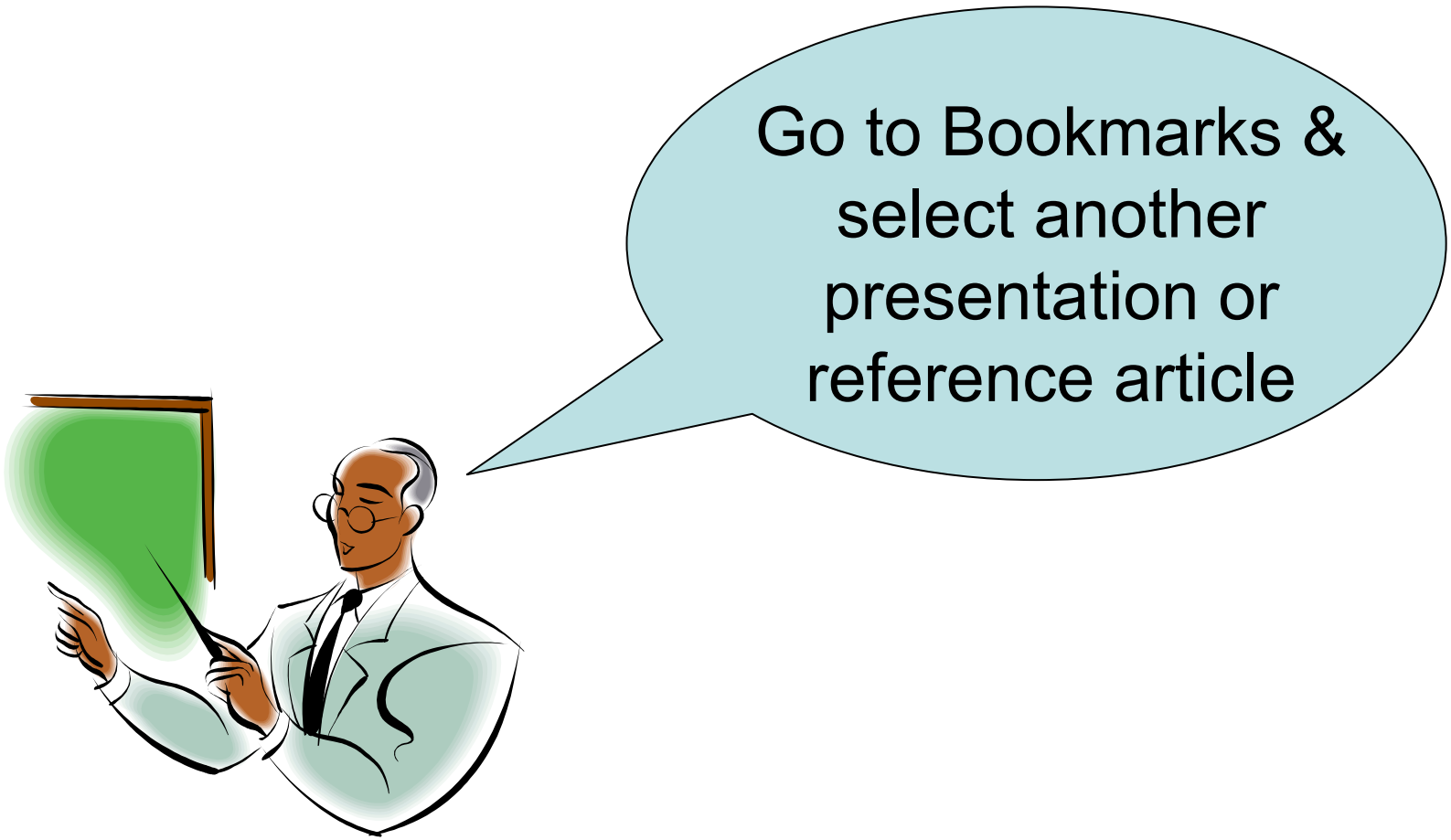
c. Any systemic reaction to AIT will be annotated in the patient's record. The patient will undergo re-assessment by an Allergist before AIT is resumed.

8. **Training/Certification:**

Those providing allergen immunotherapy in the _____ Clinic will be trained personnel. It is highly desirable that physicians, nurses, and technicians be certified by either the US Air Force's Introduction to Allergy/Allergy Extender Program or through the US Army's Walter Reed Immunization Technicians' Course. If this is not operationally feasible, then for the purpose of providing allergen immunotherapy only, the Navy's "Remote Site Allergen Immunotherapy Administration Course" (via electronic media) coupled with diligent oversight by the Clinic's Physician-In-Charge must suffice.

All personnel involved in the administration of allergen immunotherapy will be expected to participate in annual refresher training. Documentation of annual competency assessment and quarterly allergy treatment record review is mandatory.

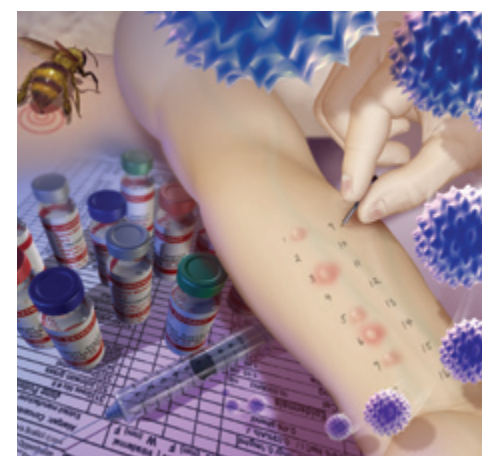
End of Selection



Allergen Immunotherapy

JENNIFER L. HUGGINS, M.D., and R. JOHN LOONEY, M.D.
University of Rochester School of Medicine and Dentistry, Rochester, New York

Allergen immunotherapy (also called allergy vaccine therapy) involves the administration of gradually increasing quantities of specific allergens to patients with IgE-mediated conditions until a dose is reached that is effective in reducing disease severity from natural exposure. The major objectives of allergen immunotherapy are to reduce responses to allergic triggers that precipitate symptoms in the short term and to decrease inflammatory response and prevent development of persistent disease in the long term. Allergen immunotherapy is safe and has been shown to be effective in the treatment of stinging-insect hypersensitivity, allergic rhinitis or conjunctivitis, and allergic asthma. Allergen immunotherapy is not effective in the treatment of atopic dermatitis, urticaria, or headaches and is potentially dangerous if used for food or antibiotic allergies. Safe administration of allergen immunotherapy requires the immediate availability of a health care professional capable of recognizing and treating anaphylaxis. An observation period of 20 to 30 minutes after injection is mandatory. Patients should not be taking beta-adrenergic blocking agents when receiving immunotherapy because these drugs may mask early signs and symptoms of anaphylaxis and make the treatment of anaphylaxis more difficult. Unlike antiallergic medication, allergen immunotherapy has the potential of altering the allergic disease course after three to five years of therapy. (Am Fam Physician 2004;70:689-96,703-4.



Allergen immunotherapy involves subcutaneous injections of gradually increasing quantities of specific allergens to an allergic patient until a dose is reached that will raise the patient's tolerance to the allergen over time, thereby minimizing symptomatic expression of the disease. Because the proteins and glycoproteins used in allergen immunotherapy are extracted from materials such as pollens, molds, pelt, and insect venoms, they were originally called allergen extracts. In 1998, the World Health Organization (WHO) proposed the term "allergen vaccine" to replace "allergen extract," because allergen immunotherapy is an immune modifier just as vaccines are.[1]

The efficacy of allergen immunotherapy has been known since 1911, when Noon injected an extract of grass pollen into a person in England whose allergic symptoms coincided with the pollination of grass.[2] Since then, controlled studies have shown that allergen immunotherapy is effective in patients with allergic rhinitis, allergic conjunctivitis, allergic asthma, and allergic reactions to Hymenoptera venom.[3-6] Patients with one or more of these diagnoses are considered for immunotherapy if they have well-defined, clinically relevant allergic triggers that markedly affect their quality of life or daily function, and if they do not attain adequate symptom relief with avoidance measures and pharmacotherapy. Despite proven efficacy, the exact mechanism of allergen immunotherapy remains unknown.

Selection of Patients

To make a definitive diagnosis of allergy, IgE-mediated, type I, immediate-hypersensitivity

skin testing typically is performed by scratching diluted allergen into the skin surface or by injecting it intradermally. A positive skin test reaction reflects the presence of specific IgE antibodies to the tested allergen, and a correlation of the specific IgE antibodies with the patient's symptoms, suspected triggers, and allergen exposure is definitive. In vitro, allergen-specific immunoassays to detect serum IgE antibodies are less sensitive than skin testing but may be used in patients with skin diseases that would obscure skin testing results or in those who cannot stop taking medications that suppress the skin test response. The circumstances in which allergen immunotherapy is particularly useful are summarized in *Table 1*. The allergens for which immunotherapy is known to be effective are Hymenoptera venom,[5] pollens,[5,6] cat dander,[7] dust mites,[8] cockroaches,[9] and fungi.[10] Allergy immunotherapy is not efficacious for atopic dermatitis, urticaria, or headaches, and cannot be used for food allergies because the risk of anaphylaxis is too great.

Type 1 immediate-hypersensitivity skin testing with clinical correlation is used to diagnose a specific IgE-mediated allergy.

TABLE 1
Best Indications for Immunotherapy

Allergic rhinitis, conjunctivitis, or allergic asthma
History of a systemic reaction to Hymenoptera and specific IgE antibodies to Hymenoptera venom
Patient wishes to avoid the long-term use or potential adverse effects of medications
Symptoms are not adequately controlled by avoidance measures or medications
Cost of immunotherapy will be less than cost of long-term medications

Benefits

Durham and colleagues[11] conducted a randomized, double-blind, placebo-controlled trial to look at effects in patients who had received three to four years of immunotherapy. They were able to demonstrate a marked reduction in allergy symptom scores and antiallergic medication usage, as well as an alteration in the natural course of allergic disease. Preliminary reports suggest that immunotherapy for allergic rhinitis may reduce the risk for later development of asthma in children.[12,13] In addition, early treatment with allergen immunotherapy in children who were sensitive only to house dust mites reduced development of sensitivity to other allergens.[14] In contrast to the use of antiallergic medication, allergen immunotherapy has the potential to alter the natural course of allergic disease and prevent progression or development of multiple allergies. Consequently, many allergists have suggested its use earlier in the course of allergic disease.

In 2000, the Immunotherapy Committee of the American Academy of Allergy, Asthma, and Immunology (AAAAI) provided a five-year cost comparison of medication usage and single-injection allergen immunotherapy for allergic rhinitis. The cost of medications is much greater than that of single-injection immunotherapy. Long-term costs deriving from the morbidity and complications of allergic diseases are not established, but allergies usually begin early in life and persist if not treated with allergen immunotherapy. A reasonable assumption is that allergen immunotherapy dramatically lowers the cost of treating allergic diseases.

The Authors

JENNIFER L. HUGGINS, M.D., is a fellow in allergy/immunology and rheumatology at the University of Rochester School of Medicine and Dentistry, Rochester, N.Y. She received her medical degree from the University of Kansas School of Medicine, Kansas City, Kan. Dr. Huggins completed postdoctoral training in pediatrics at Baylor University in Houston, and in internal medicine at the University of Rochester School of Medicine and Dentistry. She is board-certified in internal medicine and pediatrics.

R. JOHN LOONEY, M.D., is associate professor of medicine and director of the Allergy and Immunology training program at the University of Rochester School of Medicine and Dentistry, where he also received his medical degree and completed postdoctoral training in internal medicine, infectious diseases, and immunology. He is board certified in infectious diseases, allergy and immunology, and rheumatology.

Address correspondence to Jennifer L. Huggins, M.D., University of Rochester, Allergy/Immunology/Rheumatology Fellow, 601 Elmwood Ave., Box #695, Rochester, NY 14642 (e-mail: Jennifer_Huggins@urmc.rochester.edu) Reprints are not available from the authors.

Standardization, Storage, and Mixing of Allergen Vaccines

Ideally, vaccines should be standardized with a defined potency and labeled with a common unit.[15] Such standardization would eliminate the variability in vaccines and allow for safer and more effective dosing. The Bioequivalent Allergy Unit (BAU), which is assigned by the U.S. Food and Drug Administration based on quantitative skin testing performed on a reference population of allergic patients known to be highly skin-test–reactive to that allergen, reflects clinical potency and is currently used for standardization of vaccines.

Standardized allergens available in the United States include cat dander, grass pollens, dust mites, and short ragweed pollen. Unstandardized vaccines may vary widely in biologic activity based on manufacturer and by lot, depending on the allergen content of the raw material and the conditions of extraction. Furthermore, the labeling conventions of Protein Nitrogen Units (PNUs) or weight by volume (wt/V) reflect protein content but not allergenic potency. Research is underway on new technologies for DNA and protein analysis that would allow an allergen vaccine to be characterized by the content of the major allergen and the consistency of each lot to be monitored accurately.

Vaccine strength is maintained by a number of procedures, including lyophilization and reconstitution with a stabilizer that contains an antimicrobial agent. A volume effect can occur as a result of adherence of the allergen to the vial surface; the larger the surface area of the vial, the more allergen is lost. Glycerol and human serum albumin (0.03 percent) are used to mitigate the volume effect. Glycerol has the added advantage of being an antimicrobial agent. At a concentration of 50 percent, glycerol inhibits enzymatic degradation of the allergens, but it may be irritating at this concentration. The combination of human serum albumin as a stabilizer and phenol as an antimicrobial additive often is used. However, human serum albumin typically is refused by patients who are Jehovah's Witnesses.

The maintenance concentrate is the dose of vaccine considered to be therapeutically effective for each of its constituent components.

Vaccines must be stored properly to preserve biologic activity *(Table 2)*.[16,17] Vaccines should be refrigerated at 4°C (39.2°F) because storage at ambient room temperature results in loss of potency within weeks, with degradation occurring within days at higher temperatures. Critical to vaccine potency is the dilution effect: highly concentrated vaccines are more stable than dilute vaccines.[18] The vaccine label should always be checked for the expiration date.

For immunotherapy to be effective, an optimal dose of each allergen must be determined. When a patient has multiple sensitivities caused by related and unrelated allergens, vaccines containing mixtures of these allergens may be prescribed. As multiple vaccines are mixed, not only will the concentration of each allergen be decreased, but certain allergens will interact. For example, fungi, dust mites, insect venoms, and cockroach have high proteolytic enzyme activity and may be combined with each other but should not be mixed with other allergens. Insect venoms usually are given alone.

TABLE 2
Factors Affecting Allergen Vaccine Potency

Time (always check the expiration date)
Storage temperature
Concentration
Volume of the vial
Type and number of allergens in the vial
Diluent used
Preservatives added

Information from references 16 and 17.

Vaccine Administration

The maintenance concentrate is the dose of vaccine that is considered to be therapeutically effective for each of its constituent components. The maintenance concentrate

TABLE 3
Required Information on Vaccine Vials

Patient's name, date of birth, and patient number
Generalized content of the vaccine*
Expiration date
Dilution from maintenance concentrate in volume per volume (v/v)
Number identifier†
Appropriate colored caps‡

**—Specific contents of each vaccine should be written on a standardized form similar to the "Immunotherapy Mix Components" form found online at: http://www.aaaai.org.*
†—In the numbering system, the maintenance concentrate should always be number 1; subsequent dilutions should be numbered from the maintenance concentrate.
‡—The color-coding system should always start with red for the maintenance concentrate followed by yellow, blue, green, and silver, in that order.

Information from reference 18.

should be determined by a prescribing allergist and clearly written on a standardized Maintenance Concentrate Prescription Form (available online at http://www.aaaai.org). An optimal maintenance dose in the range of 5 to 20 mcg of major allergen per injection correlates with efficacy. Maintenance concentration is usually achieved by administering between 18 and 27 serial dose increments at weekly intervals (a build-up schedule written by the allergist) until the maintenance concentrate is achieved. In a typical build-up schedule, the patient will reach the maintenance concentrate in six months, but patients with a higher degree of allergen sensitivity may require a longer build-up phase. The maintenance dose usually is administered every three to four weeks, and maximum benefit typically is achieved in four to five years. Some patients will note early improvement in their symptoms, but long-term benefit seems to be related to the cumulative dose of vaccine given over time.

To reduce administration errors, the AAAAI recommends a universal, consistent, and redundant labeling system for every vial *(Table 3)*.[18]

Some circumstances warrant adjustments in the dosage schedule. In these situations, communication between the family physician and the prescribing allergist is encouraged to increase safety and avoid unexpected reactions. If the interval between injections is prolonged *(Table 4)*, the dose of vaccine must be reduced; when a new maintenance vial is obtained from the manufacturer, a dose reduction of 50 percent is recommended. For example, 0.5 mL of 1:500 V/V dilution should be reduced to 0.25 mL of 1:500 V/V dilution. The dose is increased every seven to 14 days until the maintenance dose is reached again. No evidence-based guidelines for dose adjustments following local, systemic, or delayed reactions are available, and the allergist should provide treatment suggestions for each of these reactions *(Table 5)*.

Listed in *Table 6* are items that should be reviewed before injecting the patient. The desired injection site is the outer aspect of the upper arm, midway between the shoulder and the elbow in the groove between the deltoid and triceps muscles. The injection is given subcutaneously, preferably with a 26- or 27-gauge needle; if blood is aspirated initially, the vaccine should not be injected. The plunger on the syringe should be depressed at a rate that does not result in wheal formation or excessive pain. Mild pressure should be applied to the injection site for about one minute, and a bandage may be placed if needed. Rubbing the injected area causes rapid absorption and should be avoided.

TABLE 4
Sample Adjustment to Immunotherapy Following Interruption of Dosage Schedule

Weeks from last injection	*Dosage adjustment**
6	Repeat previous dose.
7	Drop back two increments.
8	Drop back three increments.
9	Check with allergist.

NOTE: *Patients on maintenance therapy (injections every three to four weeks). Increments are provided by the allergist.*

**—Patients must return weekly until they reach the maintenance concentrate again.*

Safety Issues

Allergen immunotherapy is safe, but the potential for an adverse reaction is always

present. Although these reactions are rare, they can be life-threatening. In 1924, Lamson reported the first case of death following immunotherapy.[19] A statistical review of the literature about systemic reactions following allergen immunotherapy by Lockey and colleagues[20] found that severe systemic reactions occurred in less than 1 percent of the patients receiving conventional immunotherapy in the United States. From 1985 to 1993 in the United States, 52.3 million administrations of immunotherapy resulted in 35 deaths. These numbers equate to a mortality incidence of less than one per 1 million.[21]

Patients with medical conditions that reduce their ability to survive systemic allergic reactions are not candidates for allergen immunotherapy. Examples of such conditions include chronic lung disease with a forced expiratory volume in one second (FEV_1) of less than 50 percent, beta-blocker or angiotensin-converting enzyme (ACE) inhibitor therapy, unstable angina or myocardial infarction, uncontrolled hypertension, and major organ failure. Allergen immunotherapy also cannot be used in patients who would have difficulty reporting signs and symptoms of a systemic reaction, such as children younger than three or four years. In addition, beta-blocker or ACE-inhibitor therapy may mask early signs of anaphylaxis. Patients who have not been compliant with other forms of therapy are not likely to be compliant with immunotherapy, thus necessitating frequent alteration in dosage schedules and increasing the chance for errors. Patients should be assessed with each injection for newly acquired risks that may not have been present at the beginning of allergen immunotherapy.

Patients with severe, poorly controlled asthma are at higher risk for systemic reactions to immunotherapy injections than patients with stable, well-controlled asthma.[20] Some physicians measure peak expiratory flow readings in all patients with asthma before administering allergen immunotherapy and withhold injections if the reading is less than 70 percent of predicted. Other measures that should be performed to minimize the risk of adverse reactions to allergen immunotherapy are listed in *Table 6*.

Because a systemic reaction occurring during pregnancy may produce severe fetal hypoxia or precipitate premature uterine contractions, immunotherapy should not be initiated during pregnancy.[18] However, immunotherapy can be maintained during pregnancy provided the patient is tolerating and benefiting from the injections.

TABLE 5
Potential Adverse Reactions to Allergy Vaccines and Suggested Treatment

Adverse reaction	*Suggested treatments*
Local reaction	
Common, occurs at the injection site, IgE-mediated, manifested primarily by wheal and flare with pruritus, usually begins 20 to 30 minutes after injection	Local cold pack; oral antihistamine; topical steroid; if reaction recurs, consider premedication with an antihistamine; rinse the syringe with diphenhydramine (Benadryl) or epinephrine before vaccine; consult allergist for dose adjustment
Large local induration	
Occurs at injection site, IgG complex (Arthrus) reaction, manifested by pain, tenderness, and hard swelling	Oral steroids, nonsteroidal anti-inflammatory drug, oral antihistamine
Systemic reactions	
Low incidence (< 0.05 to 3.5 percent), manifestations can include: urticaria, angioedema, increased respiratory symptoms (nasal or pulmonary), increased ocular symptoms, and hypotension.	Tourniquet above injection site; aqueous epinephrine 1:1,000 IM: (adults, 0.3 mL; children, 0.01 mL per kg; readminister every 10 minutes if systemic symptoms persist, up to three times); diphenhydramine, IM or IV (adults, 25 to 50 mg; children, 1 to 2 mg per kg); histamine H_2 receptor blockers IV or orally for epinephrine-resistant hypotension; IV fluids or vasopressors, as needed; consider glucagon if patient is taking a beta blocker; consult allergist before any additional doses.
Delayed reaction	
May be local or systemic	Oral antihistamine (liquid is preferred); prednisone, 5 to 20 mg orally every 12 hours for two doses (depending on the patient's weight); epinephrine is not helpful; consult allergist for dose adjustment.

IM = intramuscular; IV = intravenous.

TABLE 6
Checklist for Safe Vaccine Administration

Identify the patient.
Analyze the health status of the patient before every injection. The risk of anaphylaxis is increased if the patient:
Has a fever, is acutely ill, or has a newly reported illness.
Is having an exacerbation of asthma or respiratory difficulties.
Is having an exacerbation of allergy symptoms.
Is taking new medications, namely beta blockers and angiotensin-converting enzyme inhibitors.
Inquire about any reactions occurring with the previous injection and consult with the allergist about appropriate adjustments to therapy.
Institute a checklist to reduce clerical and nursing errors:
Identify the patient's record by name and, preferably, photograph.
Check the identity, expiration date, concentration, and cap color of the vaccine vial.
Record the proper dose of vaccine on the immunotherapy record and the arm used to administer the vaccine. Alternate arms.
Draw the proper dose.
Administer the vaccine only after the patient's identity has been rechecked by comparing the patient's name with the name on the vial from which the vaccine is taken.
Remind the patient to remain in the office for 30 minutes following the injection. Check the injection site before the patient leaves.
Strenuous exercise one hour before and two hours after the injection increases the chance of anaphylaxis and should be avoided.
Document any adverse reactions.

TABLE 7
Equipment and Medications Needed to Treat Anaphylaxis

Stethoscope
Tourniquet
Equipment for monitoring blood pressure
Large-bore (14-gauge) IV catheter
Epinephrine, 1:1,000 for IM injection
Oxygen
Oral airway
Equipment for administering IV fluids
H_1 and H_2 antihistamines for injection
Corticosteroid for IV injection
Vasopressor
Glucagon for use in patients receiving beta-adrenergic blocking agents

IV = intravenous; IM = intramuscular.

The immunotherapy dose should not be increased in a pregnant patient until after delivery.

Anaphylaxis is the most serious risk related to allergen immunotherapy. The vaccines must be administered in a setting with trained professionals who are equipped to recognize and treat anaphylaxis[22] *(Table 7)*. A retrospective study found that most systemic reactions occurred within 30 minutes of injection.[23] Hence, the current recommendation is to allow at least 20 to 30 minutes of observation following an injection. Patients who have had a systemic reaction after more than 30 minutes following an injection require longer observation; in addition, they should be given injectable epinephrine to carry and instructions about how to use it. Nonetheless, reactions may occur without warning signs or symptoms, and documentation of informed consent must be obtained from the patient *(Figure 1)*.

Assessment of Immunotherapy Efficacy

After one year on a maintenance dose, clinical improvement should be apparent.[24] The therapy often may be discontinued after three to five years because by then the disease course has been altered.[11] Evaluation by an allergist, at least annually, should include monitoring of adverse reactions, assessment of efficacy, reinforcement of compliance and safe administration of immunotherapy, and determination of whether adjustments in the dosing schedule or allergen content are necessary.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

The authors thank Barbara J. Kuyper, Ph.D., and David M. Siegel, M.D., for assistance with the manuscript.

REFERENCES

1. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Geneva: January 27-29, 1997. Allergy 1998;53(44 suppl):1-42.
2. Noon L, Cantab BC. Prophylactic inoculation against hay fever. Lancet 1911;1:1572-4.
3. Pichler CE, Helbling A, Pichler WJ. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. Allergy 2001;56:301-6.

Informed Consent

Date:

Patient name:

Date of birth:

I have been made aware by _____ of the following:

During the build-up phase of my allergen immunotherapy (allergy injections), I agree to come every seven to 10 days to safely increase my vaccines at every visit. If more than 10 days have passed since my last visit, my dose will be adjusted as necessary.

Local reactions are not uncommon. I will monitor the size of the reactions and the length of time they last and inform the medical staff.

Generalized reactions occur less commonly and may include symptoms of itching of the skin; sudden itching of the nose, mouth, ears, and throat; hives, wheezing, coughing, tightness of the chest, plugging of the nose, or sneezing. Although rare, serious reactions may result in significant respiratory reactions or anaphylactic shock, which may be life-threatening. A serious reaction usually occurs within 30 minutes after an injection.

I agree to remain in the medical facility for 30 minutes after my injections and to immediately report any symptoms to the medical staff.

I have had the opportunity to have all of my questions about allergen immunotherapy answered to my satisfaction. I have been informed of the potential risks and benefits of allergen immunotherapy and available alternative therapies.

Signature of patient or guardian: _____

Date: _____

Signature of witness: _____

Date: _____

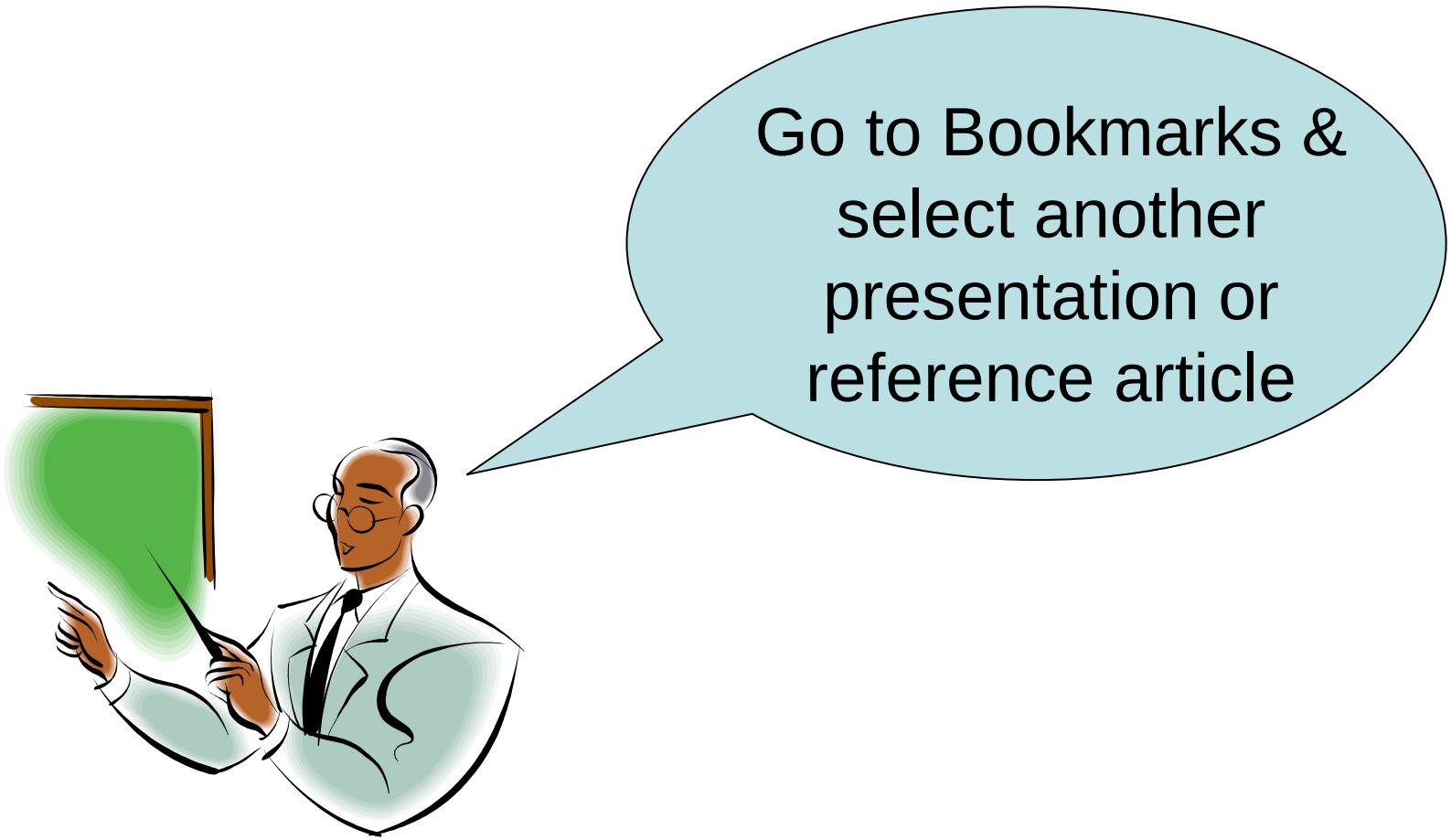
Figure 1. Example of informed consent form for allergen immunotherapy.

Strength of Recommendations

Key clinical recommendation	SOR labels	References
Allergen immunotherapy is effective in patients with allergic rhinitis, allergic conjunctivitis, allergic asthma, and allergic reactions to Hymenoptera venom.	A	3, 4, 5, 6
The allergens for which immunotherapy is known to be effective are Hymenoptera venom, pollens, cat dander, dust mites, cockroach, and fungi.	A B	5, 6, 8, 10 7, 9
In patients who had received three to four years of immunotherapy, a marked reduction in allergy symptom scores and antiallergic medication usage, as well as an alteration in the natural course of allergic disease, was demonstrated.	A	11
Immunotherapy for allergic rhinitis may reduce the risk for later development of asthma in children.	B	12, 13
Early treatment with allergen immunotherapy in children who were sensitive only to house dust mites reduced development of sensitivity to other allergens.	C	14
Patients with severe, poorly controlled asthma are at higher risk for systemic reactions to immunotherapy injections than patients with stable, well-controlled asthma.	B	20

4. Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31.
5. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, single or double-blind, placebo-controlled studies. Clin Ther 2000;22:329-41.
6. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151:969-74.
7. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind, placebo-controlled trial. Clin Exp Allergy 1997;27:860-7.
8. Olsen OT, Larsen KR, Jacobsan L, Svendsen UG. A one-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. Allergy 1997;52:853-9.
9. Kang BC, Johnson J, Morgan C, Chang JL. The role of immunotherapy in cockroach asthma. J Asthma 1988;25:205-18.
10. Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. I. Clinical results. Allergy 1986;41:131-40.
11. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.
12. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.
13. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000;162:2048-52.
14. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3.
15. Nelson HS. The use of standardized extracts in allergen immunotherapy. J Allergy Clin Immunol 2000;106(1 pt 1):41-5.
16. Nelson HS. Effects of preservatives and conditions of storage on the potency of allergy extracts. J Allergy Clin Immunol 1981;67:64-9.
17. Nelson HS, Ikle D, Buchmeier A. Studies of allergen extract stability: the effects of dilution and mixing. J Allergy Clin Immunol 1996;98:382-8.
18. Joint Task Force on Practice Parameters. Allergen immunotherapy: a practice parameter. Ann Allergy Asthma Immunol 2003;90(1 suppl 1):1-40.
19. Lamson RW. Sudden death associated with injection of foreign substances. JAMA 1924;82:1090.
20. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87(1 suppl 1):47-55.
21. Turkeltaub P. Deaths associated with allergenic extracts. FDA Medical Bulletin 24, May 1994.
22. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000;30:1144-50.
23. Greenberg MA, Kaufman CR, Gonzalez GE, Rosenblatt CD, Smith LJ, Summers RJ. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986;77:865-70.
24. McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of *Dermatophagoides pteronyssin*us in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol 1990;86(4 pt 1):521-31.

End of Selection



Evaluation of near-fatal reactions to allergen immunotherapy injections

Hetal S. Amin, MD,[a] Gary M. Liss, MD,[b] and David I. Bernstein, MD[a]

Cincinnati, Ohio, and Toronto, Ontario, Canada

Background: The overall incidence of near-fatal reactions (NFRs) after immunotherapy injections is unknown. Investigation of NFRs might identify preventive strategies that could avert fatal immunotherapy reactions.
Objective: We sought to determine the incidence and characteristics of NFRs to allergen immunotherapy.
Methods: In a brief survey of fatal reactions (FRs) and NFRs administered to practicing allergists, 273 of 646 respondents reported NFRs after immunotherapy injections; a NFR was defined as respiratory compromise, hypotension, or both requiring emergency epinephrine. Respondents were mailed a 105-item questionnaire regarding the details of NFRs and circumstances of these events.
Results: During the period from 1990 through 2001, the incidence of unconfirmed NFRs was estimated at 23 per year (5.4 events per million injections). There were 68 confirmed NFRs on the basis of responses to the long survey, with a mean case incidence of 4.7 per year or 1 NFR per million injections. Asthma was present in 46% of near-fatal reactors and in 88% of fatal reactors identified in this study. Hypotension was reported in 80% and respiratory failure occurred in 10% of NFRs and exclusively in asthmatic subjects. Epinephrine was delayed or not administered in 6% of NFRs versus 30% of reported FRs (OR, 7.3; 95% CI, 1.4-39.8; $P = .01$).
Conclusions: Confirmed NFRs were 2.5 times more frequent than FRs. Favorable outcomes of NFRs when compared with FRs could be related to lower asthma prevalence and appropriate management of life-threatening anaphylaxis.
(J Allergy Clin Immunol 2006;117:169-75.)

Key words: *Immunotherapy, anaphylaxis, near-fatal reactions, asthma, epinephrine*

Abbreviations used
AAAAI: American Academy of Allergy, Asthma and Immunology
FR: Fatal reaction
NFR: Near-fatal reaction
OR: Odds ratio

Immunotherapy with subcutaneous injections of aeroallergen extracts has proved beneficial in reducing symptoms of allergic rhinitis and asthma.[1] However, injection-related systemic reactions reportedly occur in 5% to 7% of patients receiving build-up and maintenance injections of allergen immunotherapy in North America.[2-4] In these surveys there were few if any descriptions of serious near-fatal systemic reactions.[3,4] In North America several studies have been conducted over the past 20 years with the purpose of characterizing and estimating the incidence of fatal reactions (FRs) to immunotherapy.[5,6] In the first of these surveys, Lockey et al[5] reported 24 FRs that occurred between 1973 and 1984 and estimated that 1 FR occurred in every 2.8 million injections. Subsequently, Reid et al[6] described 15 immunotherapy-related fatalities that transpired between 1985 and 1989 and estimated 1 fatality in every 2.0 million injections. Recently, we reported the results of an immunotherapy fatality survey that documented 41 FRs between 1990 and 2001, and from these data, we estimated 1 FR in every 2.5 million injections.[7]

Despite characterization of susceptibility factors for immunotherapy fatalities, dissemination of earlier survey findings, and publication of immunotherapy practice parameters, the apparent incidence rate of immunotherapy-related deaths has not changed in the past 40 years.[8] Although characteristics of immunotherapy-related fatalities have been well defined, there are no data that define factors that contribute to serious near-fatal reactions (NFRs). Characterization of NFRs and effective interventions that prevent fatal outcomes could be useful in formulating guidelines aimed at reducing future fatal events. We conducted a retrospective cross-sectional national survey of immunotherapy-induced NFRs; the objectives were to estimate the incidence of NFRs, define characteristics and treatment of NFRs, and compare characteristics of NFRs with those of FRs.

METHODS

The first phase of the study was initiated with a brief 6-question survey distributed to all physician members of the American Academy of Allergy, Asthma and Immunology (AAAAI) by fax,

From [a]the Department of Internal Medicine, Division of Immunology and Allergy, University of Cincinnati; and [b]Gage Occupational and Environmental Health Unit, Department of Public Health Sciences, University of Toronto.

Supported by the Immunotherapy Committee of the American Academy of Allergy and Clinical Immunology (AAAAI).
Received for publication July 8, 2005; revised October 9, 2005; accepted for publication October 12, 2005.

Reprint requests: David I. Bernstein, MD, University of Cincinnati, PO Box 670563, Cincinnati, OH 45267-0563. E-mail: bernstdd@ucmail.uc.edu.

0091-6749/$32.00

doi:10.1016/j.jaci.2005.10.010

e-mail, and the organizational newsletter between 2000 and 2001. The short survey (available in the Online Repository of this article at www.jacionline.org) queried about both FRs and NFRs associated with immunotherapy injections, and results of fatal events have already been published.[7] Individuals who did not respond initially were resent the form at least twice; one completed survey response was requested from each allergy practice. In the survey a NFR was defined as severe respiratory compromise, hypotension, or both requiring emergency treatment with epinephrine. On the basis of billing codes, respondents were asked to provide the total number of immunotherapy injections administered in their respective clinics during the previous 1 and 3 years.

Physicians who reported FRs to immunotherapy or skin testing in the short survey were subsequently sent an 87-item questionnaire (available in the Online Repository of this article at www.jacionline.org), which they were asked to complete. Results of the latter survey of FRs have been published.[7] In this final phase of the study, conducted during 2003 and 2004, detailed 105-item questionnaires were sent to 273 physicians who had reported NFRs on the initial short survey. Key elements captured in the latter questionnaire included (1) demographics; (2) clinical indications for starting immunotherapy; (3) classification of asthma severity, asthma exacerbations, emergency department and hospital visits for acute asthma, and oral steroid requirements; (4) clinical setting where events occurred (allergist vs primary care office); (5) dosing errors, allergen extract concentration, and schedule for immunotherapy administration; (6) timing of immunotherapy injections relative to patient's pollen season; (7) prior local, systemic, or both injection-related reactions; (8) observance by patients of postinjection waiting periods; (9) time of onset of reactions; (10) clinical manifestations of NFRs; (11) treatment of NFRs, including details of epinephrine administration; and (12) physicians' assessments of key factors leading to NFRs.

As described in our previous article on FRs, estimates of incidence rates of NFRs per million injections were based on assumptions that injection data of 646 respondents were representative of 2404 AAAAI member physicians. Analysis of the data was performed with SAS (version 8.1; SAS Institute, Cary, NC) and Epistat (Epistat Services, Richardson, Tex). Because the number of injections was not normally distributed, geometric mean data are presented and used in the calculation of incidence rates. *Confirmed NFRs* refers to the 68 cases reported in both the short and long surveys, whereas *unconfirmed NFRs* are those that were only reported on the initial short survey.

RESULTS

The sample represented 646 (27%) of 2404 clinical practices affiliated with the AAAAI who responded to the short survey. All were located in the United States and Canada. Physicians in 273 practices identified a NFR. Of these, 70 respondents completed the 105-item questionnaire after repeated requests were made through e-mail, fax, and personal communication through the AAAAI. No NFRs to skin testing were reported. There was one report of a vasovagal response after an immunotherapy injection and a second patient who experienced a mild systemic urticarial reaction. The results of 68 reported events meeting the NFR definition are presented below.

Incidence of NFRs

Data from the initial short survey used to estimate the mean annual number of injections administered in allergy practices reporting no systemic reactions, NFRs, and FRs have already been published.[7] As reported in the latter article, the geometric mean number of injections administered over 3 years was highest in the practices reporting FRs (mean number, 27,447 injections), followed by those experiencing NFRs (mean number, 23,860 injections). The clinic groups that reported no life-threatening reactions administered a significantly lower geometric mean number of immunotherapy injections (15,835) compared with the groups reporting FRs and NFRs ($P = .016$, ANOVA). Pairwise comparison indicated that the mean number of injections was significantly greater in the near-fatal reactor group versus the nonreactor group ($P < .05$). Similar comparisons were significant among all 3 groups when the mean number of injections administered during 1 year was analyzed.

On the basis of directly reported NFRs (68 cases) and the geometric mean number of injections administered for all respondents, the incidence of confirmed NFRs was 1.0 event per million injections. This rate was approximately 2.5 times greater than the incidence of confirmed FRs (1 per 2.54 million injections). The incidence of unconfirmed NFRs was 5.4 events per million injections. The average incidence of confirmed NFRs was 4.7 events per year, which was 2.8 times more frequent than the incidence of confirmed FRs (1.7 cases per year) during the same reporting period. The average incidence rate of (all) unconfirmed NFRs was estimated at 23 cases per year, which is 5.4 times higher than that of confirmed NFRs.

Patient characteristics

The mean age of the nonfatal reactors was 35.9 years (median, 37.5 years; range, 5-70 years), including 35 (51%) male subjects and 33 (49%) female subjects. Six (9%) NFRs were reported in children 12 years of age or younger (range, 5-12 years). Five of the children were given diagnoses of asthma, one of whom (an 11-year-old subject) had respiratory failure requiring intubation.

Reported comorbid conditions were rare and included 1 patient with diabetes and 5 patients with hypertension. At the time of the NFR, 2 patients were receiving concomitant angiotensin II receptor blockers, and 1 patient was receiving a β-blocker (atenolol, 25 mg daily). The latter patient experienced hives and bronchospasm that responded to inhaled albuterol and 0.3 mg of subcutaneous epinephrine; glucagon was not required. Ten (15%) patients with NFRs had reported taking H_1 blockers on the day of the NFR; there was no trend suggesting less severe reactions among those patients. There were no reports of concomitant angiotensin-converting enzyme inhibitors.

Clinical indication for immunotherapy. Indications for immunotherapy included allergic rhinitis in 33 (49%) of 68 near-fatal reactors, allergic rhinitis and asthma in 29 (43%), asthma alone in 2 (3%), and hymenoptera anaphylaxis in 4 (6%).

Asthma Severity. There were 31 asthmatic subjects, and respondents were asked to categorize asthma severity according to the National Heart, Lung, and Blood Institute classification.[9] Seventeen (55%) were categorized as

having mild intermittent or mild persistent asthma, 11 (35%) as having moderate persistent asthma, and 3 (10%) as having severe persistent asthma. Although only 20 respondents reported FEV_1 values, 8 (40%) individuals had baseline (before initiation of immunotherapy injections) FEV_1 of less than 70% of predicted values; 4 (50%) experienced respiratory failure requiring intubation during their NFRs versus 2 (17%) of 12 with FEV_1 values of greater than 70%. There were 7 (23%) asthmatic subjects treated with oral corticosteroids within the 6 months before the NFR. Nearly all asthmatic subjects (85%) were receiving inhaled corticosteroids; 5 (16%) were also receiving a concomitant long-acting β-agonist, and 4 (13%) were using leukotriene antagonists exclusively for asthma management. Two (7%) asthmatic subjects were taking oral corticosteroids at the time of the NFR, and physicians reported that 23 (74%) of 31 asthmatic subjects were compliant with recommended inhaled corticosteroids before the NFR. Furthermore, 9% had had emergency department visits for asthma in the past, and 4% had been hospitalized.

Prior reactions to allergen injections. During the 6 months preceding NFRs, local and systemic reactions were reported in 13 (19%) and 6 (9%) respondents, respectively. Prior systemic reactions in 6 patients were manifested as acute bronchospasm in 2 patients, upper airway obstruction in 1 patient, hypotension in 1 patient, and pruritus and hives in 2 patients. Epinephrine was not administered, suggesting that these systemic reactions were not perceived as serious. The next immunotherapy doses were reduced in 1 patient; the remaining 5 patients remained at the same dose that elicited the systemic reaction.

Details of immunotherapy administration

In 67 (99%) of 68 NFRs, allergen extracts were prescribed by board-certified allergists. The near-fatal injections were administered subcutaneously in all but 3 (4%) individuals who received intramuscular injections, which physician respondents attributed to administration errors. Sixty-three (93%) near-fatal events occurred in clinics of board-certified allergists who were present during the reaction; the remaining 5 (7%) NFRs occurred in primary care settings. There were no reports of NFRs in unsupervised clinics or after self-administration. Thirty-eight (58%) received near-fatal injections from maintenance extracts, and the remainder were from build-up vials. Twelve (18%) NFRs followed an initial injection from a new nonmaintenance vial, and only 2 of 68 respondents noted a recent change in allergen extract manufacturer. Nearly all (98%) of the near-fatal injections were administered from vials that were 6 months old or less. NFRs reportedly occurred during the patients' allergy season in 38 (56%) subjects, and dosing errors were reported in 15 (25%) of the near-fatal events.

Clinical manifestations of NFRs

Time of onset. Initial manifestations of NFRs began 30 minutes or less after immunotherapy injection in 65 (96%) of 68 patients, and late-onset reactions occurred in 3 individuals more than 30 minutes after immunotherapy administration. Two of the 3 latter individuals returned to the clinic 45 minutes after receiving the injection, and both experienced pruritus, hives, and bronchospasm. Epinephrine was delayed (>30 minutes) but administered in both individuals. The third patient experienced pruritus and severe hypotension 60 minutes after the injection was administered by a primary care physician; epinephrine was administered immediately on arrival.

Clinical features. Fig 1 shows the clinical manifestations of NFRs, as well as previously reported FRs from this survey.[7] Nearly all near-fatal reactors experienced hypotension (88%), but fewer had respiratory features of upper airway obstruction (41%) or bronchospasm (51%). There were 20 (30%) patients who experienced no cutaneous manifestations during NFRs (ie, urticaria, angioedema, and/or pruritus). Three (4%) individuals had late-onset reactions (occurring >30 minutes after immunotherapy administration), and 30 (44%) of 68 near-fatal reactors experienced loss of consciousness. Respiratory failure occurred in 7 (10%) of 68 near-fatal reactors, all of whom had moderate or severe asthma; 4 (57%) of 7 requiring intubation had pretreatment FEV_1 values of less than 70% of predicted value. Four of 5 near-fatal reactors who had cardiopulmonary arrest were asthmatic subjects.

Circumstances contributing to near-fatal outcomes

Respondents were queried about factors that significantly contributed to NFRs. Important contributing factors included administration of injections during the height of the allergy season (46% of respondents), allergen vaccine dosing errors (25%), less than optimal asthma control at the time of the NFR (10%), history of previous systemic reactions to allergen injections (9%), concomitant medication (eg, β-blockers; 3%), and premature clinic departure before the end of the required waiting period (3%).

Management of NFRs

One patient who experienced a NFR in a primary care clinic did not receive epinephrine and was managed with intravenous fluids and antihistamines. Eighty-two percent (56/68) of NFRs were treated within 3 minutes of onset of NFRs, and 94% received epinephrine within 20 minutes. The initial epinephrine dose was 0.3 to 0.5 mg in 58 (85%) patients, whereas 7 patients received less than 0.2 mg and 2 patients received more than 0.5 mg. Epinephrine was administered subcutaneously in 45 (66%) patients by the intramuscular route in 18 (27%) patients and by both routes in 4 (6%) patients. There was no significant difference in mean total epinephrine dose between patients receiving subcutaneous (0.6-1.0 mg) versus those receiving intramuscular (0.3-0.6 mg) dosing. Four received both subcutaneous and subsequently intramuscular epinephrine for persistent hypotension and respiratory symptoms. Three patients received intravenous epinephrine (1:10,000). Of 67 patients given epinephrine, 53 (78%) also received systemic corticosteroids, 51 (75%) received H_1

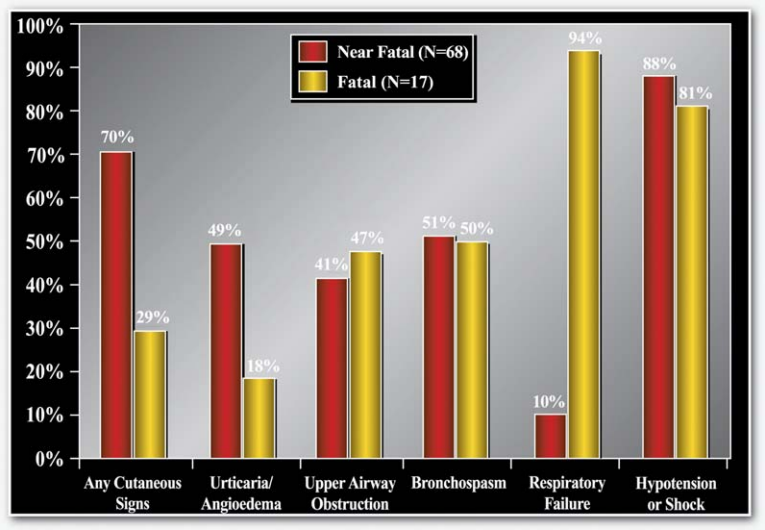


FIG 1. Comparison of clinical features during FRs and NFRs. *Any cutaneous signs* refers to hives, angioedema, and/or pruritus. *Hypotension* refers to either transient or sustained decrease in blood pressure, and *shock* refers to cardiovascular collapse.

antihistamines, 47 (69%) were given oxygen, and 28 (41%) were given intravenous fluids, and vasopressors were begun in 3 (4%) near-fatal reactors. Antihistamines and systemic corticosteroids were administered along with epinephrine in 43 (63%) NFRs.

Comparisons of near-fatal and fatal reactors

Characteristics and management of 68 patients with NFRs were compared with previously reported characteristics of 17 patients with fatal events in this survey.[7] Common items used in both fatal and near-fatal surveys facilitated these comparisons. It was noteworthy that 15 (88%) of 17 fatal reactors had been given diagnoses of asthma compared with 46% in the larger NFR group. As shown in Fig 1, a similar proportion of patients with FRs (81%) and NFRs (88%) experienced hypotension or shock. Severe airway obstruction leading to respiratory failure was far less common with NFRs. Near-fatal reactors experienced cutaneous symptoms (ie, urticaria and angioedema) more often than fatal reactors.

As shown in Fig 2, there was a higher frequency of responses for all questionnaire items reflecting poorly controlled asthma in fatal reactors. Fatal reactors were much more likely to have had a prior emergency department visit (54% vs 9%; odds ratio [OR], 12.1; 95% CI, 2.6-61.1; $P < .001$) and to have been hospitalized for asthma (61.5% vs 4%; OR, 34.7; 95% CI, 5.7-251; $P < .001$).

It is noteworthy that 93% of NFRs occurred in clinics staffed by allergists in contrast to 59% of fatal events (OR, 8.5; 95% CI, 1.98-41.3; $P = .002$). There were no NFRs in a medically unsupervised setting compared with 2 (12%) of 17 FRs that were reported with home administration of immunotherapy.

Epinephrine was delayed for longer than 20 minutes or not administered in 30% of FRs compared with 6% of NFRs (OR, 7.3; 95% CI, 1.4-40; $P = .01$). Intubation was required for respiratory failure more frequently among FRs (88%) compared with among NFRs (9%) (OR, 130.7; 95% CI, 13.9-53.5; $P < .001$).

DISCUSSION

This is the first large evaluation of NFRs caused by subcutaneous immunotherapy injections. We acknowledge that the retrospective nature of this survey might lead to recall and reporting bias. Our approach differed from those of previous studies of serious immunotherapy reactions in that we administered a brief 6-item survey to a large group of practicing allergists-immunologists to gather reports of fatal and near-fatal events.[5,6] The intent of the brief survey was to obtain a high response rate among clinicians and to capture additional information pertaining to NFRs and mean numbers of allergen injections administered in clinics of respondents. Despite multiple efforts, we achieved response rates of 27% and 25% for the short and long surveys, respectively. This degree of participation is typical for professional surveys, and the low responder rate does not diminish the importance of our findings. We also received only 5 (7%) reports of NFRs that occurred in primary care clinics; it is likely that many more might have occurred in this setting. Thus these factors are likely to result in significant underestimates of the true incidence of NFRs.

NFRs occurred in all age groups (ages 5-70 years), including 6 children 5 to 12 years of age; 1 child with respiratory failure required intubation. In the published fatality survey conducted in the initial phase of this study, FRs were also reported in 2 children with asthma, ages 5 and 12 years.[7] Our observations bear similarity to a prior study by Ostergaard et al,[10] who documented 6 serious anaphylactic reactions (3 were life-threatening) that were

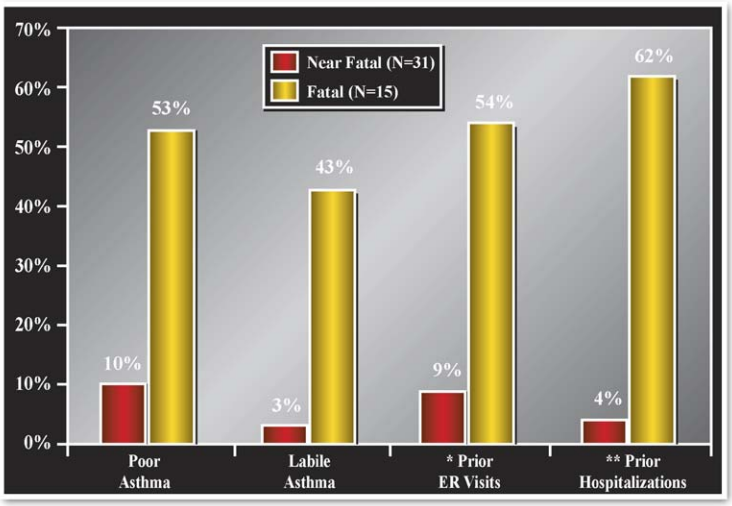


FIG 2. Comparison of asthma severity in fatal and near-fatal reactors. *OR, 12.1 (95% CI, 2.6-61.0; $P < .001$); **OR, 34.7 (95% CI, 5.7-251.1; $P < .001$). *ER*, Emergency department.

attributed to injections with maintenance doses of mold extract in 106 asthmatic children. More recent prospective studies of asthmatic children reported no serious systemic reactions to pollen, dust mite extracts, or both.[11,12] Clearly our survey indicates that NFRs and FRs occur among children and primarily in asthmatic subjects. However, there are insufficient data to estimate the risk relative to that seen in adult patients.

We estimated that one confirmed NFR occurred with every 1 million injections and at a rate that was 2.5 times greater than that found for confirmed FRs.[7] This translated into nearly 5 NFRs per year in North America. However, because unconfirmed NFRs based on responses to the brief survey alone yielded more than 5 times more cases, it is likely that analyzing ''confirmed'' NFRs (ie, long NFR survey responders) greatly underestimated the true incidence rates of NFRs. As noted in our previous report of FRs, the number of injections administered in clinics reporting NFRs was significantly greater than that in clinics reporting no serious or life-threatening immunotherapy reactions.[7] This interesting observation could be attributable to reduced probability of NFRs because of fewer overall injections or to the fact that physicians who administer fewer injections are more selective in excluding high-risk patients.

As in fatal surveys, we examined putative contributing factors. Only one of the near-fatal reactors was receiving a β-blocking agent. Interestingly, this therapy did not appear to inhibit treatment responses to epinephrine, nor was glucagon required. The infrequent use of β-blockers in this study likely reflects adherence to published immunotherapy guidelines recommending avoidance of these drugs.[8,13] Hepner et al[14] conducted a prospective study of β-blocker use in more than 3100 patients receiving immunotherapy, including 68 patients receiving β-blockers. They concluded that the risk of injection-related systemic reactions was not increased but cautioned that β-blockade might increase severity of reactions as they occur. However, current guidelines advise avoidance of immunotherapy in patients requiring β-blockers.[8] Because no patients in this study were receiving angiotensin-converting enzyme inhibitors, the effects of these agents in NFRs could not be assessed.

It was not surprising that the majority (54%) of NFRs were reported in nonasthmatic subjects, which contrasted sharply with reports of fatal reactors, most of whom had asthma that was often suboptimally controlled.[5-7,15] In our study the most severe reactions manifested by acute respiratory failure occurred in 7 patients with asthma, 4 (57%) of whom had reported baseline FEV_1 values below 70% of predicted value. Bousquet and Michel[16] have recommended that immunotherapy with aqueous extracts be withheld from such patients in light of data indicating that asthmatic subjects with FEV_1 value of less than 70% of predicted value are at greater risk for systemic reactions. This report of NFRs further demonstrates the heightened risk of life-threatening reactions in patients with asthma with moderate and severe airway obstruction.

Physician respondents identified immunotherapy administration during peak allergy seasons (46% of respondents) and dosing errors (25% of respondents) as the 2 most important factors contributing to NFRs. In a large physician survey, dosing errors were reported by most respondents and were most often attributed to misidentification of patients and injection of incorrect doses.[17] Our data suggest that dosing mistakes can have serious consequences. As with FR reports, NFRs were more common after injections from maintenance rather than build-up vials.[2,7,10] It is possible that reactions to maintenance injections might have been related to priming by natural allergen exposure, which could have enhanced sensitivity to doses of previously well-tolerated allergens. Furthermore, intramuscular administration of immunotherapy in a few responders was attributed to error in administration of immunotherapy injection. Although this is definitely in

TABLE I. Summary of key findings from the Near Fatal Reaction Survey and proposed recommendations aimed at preventing life-threatening reactions after immunotherapy injections

Study findings	Proposed recommendations
Patients with reduced FEV_1 (<70% of predicted value) experienced respiratory failure requiring intubation.	Consider withholding immunotherapy in patients with moderate or severe airway obstruction. Assess all patients for worsening asthma and monitor lung function (PEFR) before immunotherapy injections. Withhold immunotherapy injections if asthma worsens.
Prior systemic reactions were present in 9% of near-fatal reactors.	Reduce subsequent immunotherapy doses. Dispense self-injectable emergency epinephrine to all patients who are continued on immunotherapy. Consider discontinuation of immunotherapy in high-risk patients (eg, those with severe asthma).
Forty-six percent of NFRs occurred during the height of an allergy season.	Consider reduction of immunotherapy doses during relevant pollen seasons.
Dosing errors were implicated in 25% of NFRs.	Prevent dosing errors.[17] Continuing education of clinic staff. Give injections from patient-specific vials and not "off the board." Use standardized forms and protocols. Routinely check patient identity (name, birth date) before each injection. Same staff person that prepares immunotherapy injection should administer. Allow only 1 patient at a time in the injection room.
Patients depart prematurely from clinic after injections.	All patients should be required to wait 30 minutes in a medically supervised setting after immunotherapy injections.

PEFR, Peak expiratory flow rate.

contrast to usual practice, the need for continual physician and office staff education and awareness of proper administration of immunotherapy is required.

It is noteworthy that 93% of patients experienced NFRs in the offices of allergists, and there were no reports of self-administration in medically unsupervised settings.[7] This might have facilitated timely treatment of NFRs in that 94% of patients received epinephrine within 20 minutes of onset of reactions. Two late-onset NFRs were reported at 45 and 60 minutes after injections. In previous fatality surveys, most but not all FRs commenced within 30 minutes, whereas non–life-threatening systemic reactions have commonly been reported to begin at 30 to 60 minutes after injections.[4,18,19] Therefore there is disagreement about the optimal postinjection waiting period. The Joint Task Force allergen immunotherapy practice parameters have recommended a 20- to 30-minute waiting period, whereas the British Society for Allergy and Clinical Immunology has advised 60 minutes.[8,15]

Prior systemic reactions were noted in 9% of near-fatal reactors, but immunotherapy doses had been reduced in only 1 of 6 patients. According to recent immunotherapy practice parameters (there are no evidence-based guidelines for dose adjustment after systemic reactions), it is usual practice to reduce the dose or consider discontinuation of immunotherapy. This result strongly suggests that after serious systemic reactions, allergists must either reduce doses to those previously tolerated or discontinue immunotherapy altogether.[8] Those patients experiencing severe systemic reactions are considered at higher risk for future serious reactions, and physicians must consider discontinuing immunotherapy injections or, at a minimum, significantly reducing future immunotherapy doses.

Clinical manifestations of NFRs were instructive. Hypotension was common (88%), but few patients had respiratory failure (10%). This is likely explained by the low prevalence of poorly controlled asthma. Interestingly, cutaneous manifestations were absent in 30% of patients with NFRs. Taken together with absent cutaneous signs reported in 81% of FRs in this study, the absence of urticaria, angioedema, or both cannot be used as a major criterion for diagnosing life-threatening anaphylaxis.[7]

Delay or failure to administer epinephrine for immunotherapy-induced anaphylaxis has been associated with poor outcomes.[7,15] In this study timely administration of epinephrine likely contributed to nonfatal outcomes. Intramuscular epinephrine, which achieves higher plasma levels than subcutaneous epinephrine, was administered in 31% of NFRs. However, we were unable to detect any differences in clinical outcomes attributable to route of administration.[20-22] It is noteworthy that 37% of NFRs were not treated with either systemic corticosteroids or antihistamines, and this did not apparently make a difference in outcomes. However, optimal therapy for anaphylaxis

should include treatment with epinephrine, diphenhydramine, and corticosteroids.

The major findings of this survey and the proposed recommendations aimed at preventing life-threatening reactions after immunotherapy injections are listed in Table I. These recommendations address measures aimed at preventing severe reactions associated with moderate to severe airway obstruction, prior systemic reactions, reactions during the height of an allergy season, and dosing errors.

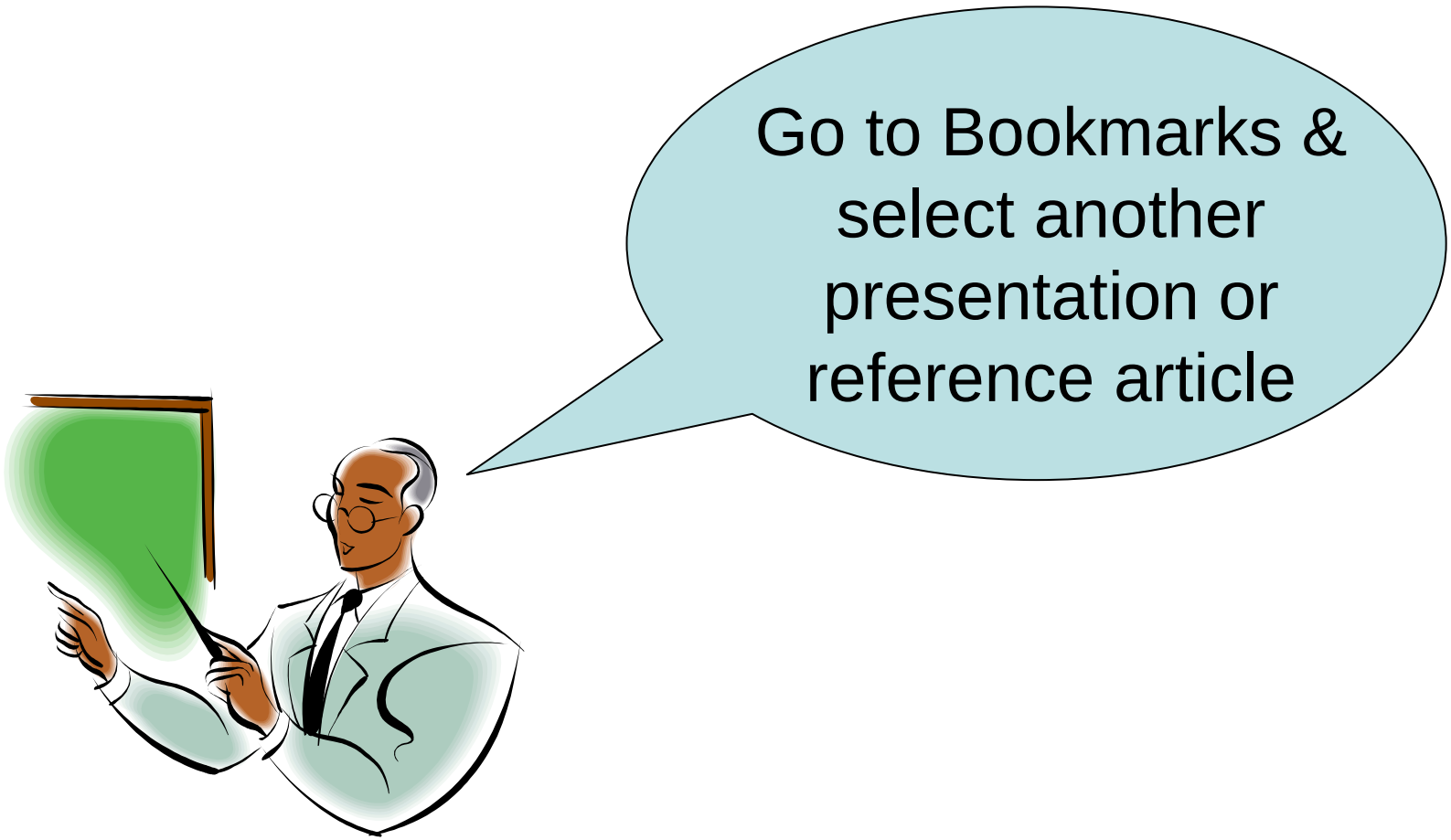
In conclusion, NFRs are not uncommon, and the incidence of fatal immunotherapy reactions has not changed in the past 40 years. More effort is needed to identify and develop methods to control risks associated with NFRs.[7] NFRs occur more frequently than FRs. Near-fatal events were managed successfully with prompt administration of epinephrine in physician-supervised clinic settings, affirming recent recommendations of the Joint Task Force Allergen immunotherapy practice parameters that immunotherapy be given in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis are assured.[8] Patients with asthma and reduced lung function (<70%) appeared to be at greatest risk for severe respiratory compromise during a NFR. This highlights the importance of weighing risks and benefits before initiating immunotherapy in patients with severe asthma and the need to carefully monitor asthma symptoms and lung function before immunotherapy injections.[8] Finally, patients who have experienced a NFR should be considered at increased risk for future FRs or NFRs, and the physician should consider the risks versus benefits of continuing immunotherapy in this setting.

We thank Eric Campbell for the illustrations and the AAAAI staff for their support.

REFERENCES

1. Abramson M, Puy R, Weiner J. Allergen immunotherapy for asthma. Cochrane Database Syst Rev 2003;4: CD001186.
2. Ragusa FV, Passalacqua G, Gambardella R, Campanari S, Barbieri MM, Scordamaglia A, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 1997;7:151-4.
3. Greenberg MA, Kaufman CR, Gonzalez GE, Rosenblatt CD, Smith LJ, Summers RJ. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986;77:865-70.
4. Ragusa VF, Massolo A. Non-fatal systemic reactions to subcutaneous immunotherapy: a 20-year experience comparison of two 10-year periods. Allerg Immunol (Paris) 2004;36:52-5.
5. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79:660-77.
6. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993;92:6-15.
7. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;113:1129-36.
8. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2003;90: 1-40.
9. National Heart, Lung and Blood Institute. Guidelines for the diagnosis and management of asthma. Lippincott Health Promot Lett 1997;2:1, 8-9.
10. Ostergaard PA, Kaad PH, Kristensen T. A prospective study on the safety of immunotherapy in children with severe asthma. Allergy 1986; 41:588-93.
11. Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 1997;7:90-7.
12. Pifferi M, Baldini G, Marrazzini G, Baldini M, Ragazzo V, Pietrobelli A, et al. Benefits of immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract in asthmatic children: a three-year prospective study. Allergy 2002;57:785-90.
13. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
14. Hepner MJ, Ownby DR, Anderson JA, Rowe MS, Sears-Ewald D, Brown EB. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. J Allergy Clin Immunol 1990;86:407-11.
15. Frew AJ. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. BMJ 1993;307:919-23.
16. Bousquet J, Michel FB. Safety considerations in assessing the role of immunotherapy in allergic disorders. Drug Saf 1994;10:5-17.
17. Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol 2004;113:1117-21.
18. Greenberg MA, Kaufman CR, Gonzalez GE, Trusewych ZP, Rosenblatt CD, Summers RJ. Late systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1988;82:287-90.
19. Altintas D, Akmanlar N, Guneser S, Burgut R, Yilmaz M, Bugdayci R, et al. Comparison between the use of adsorbed and aqueous immunotherapy material in *Dermatophagoides pteronyssinus* sensitive asthmatic children. Allergol Immunopathol (Madr) 1999;27:309-17.
20. Hughes G, Fitzharris P. Managing acute anaphylaxis. New guidelines emphasise importance of intramuscular adrenaline. BMJ 1999;319:1-2.
21. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998; 101:33-7.
22. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001; 108:871-3.

End of Selection



Allergy Treatment Record Review

Chart ID: _____ Reviewer: _____ Date: _____

	Yes	No*	N/A
1. All necessary forms present:			
a. Intake questionnaire			
b. Signed informed consent form			
c. Current allergen extract prescription			
d. Pre-shot questionnaire			
e. Treatment form			
f. Missed-dose/reaction AIT dose adjustment instruction			
2. Patient identification on all forms. Name alert on chart cover.			
3. Treatment form:			
a. Legible			
b. Drug/latex allergies documented			
c. Current prescription number & therapy start date			
d. Shot dates entered			
e. Concentration (cap color/dilution) entered			
f. Delayed reaction noted prior to administering shot			
g. Document dose verified by patient/guardian			
h. Dosages are correct per schedule with appropriate adjustments as indicated			
i. Arm(s) used noted			
j. Immediate reaction noted prior to departing clinic			
k. Entry initialed and initials correspond to signature			
4. Asthma patient:			
a. Chart flagged and minimum PF or FEV1 present			
b. PF or FEV1 recorded prior to shot			
c. No shot given and physician's note if PF/FEV1 below minimum (< 80% predicted or > 15% below baseline)			
5. Nursing notes:			
a. Dose changes documented on treatment form			
b. Systemic reactions documented:			
i. Vital signs recorded			
ii. Treatment documented			
iii. Physician note included			
iv. Patient disposition documented			

Comments (note praise-worthy findings and explain all items answered No above):

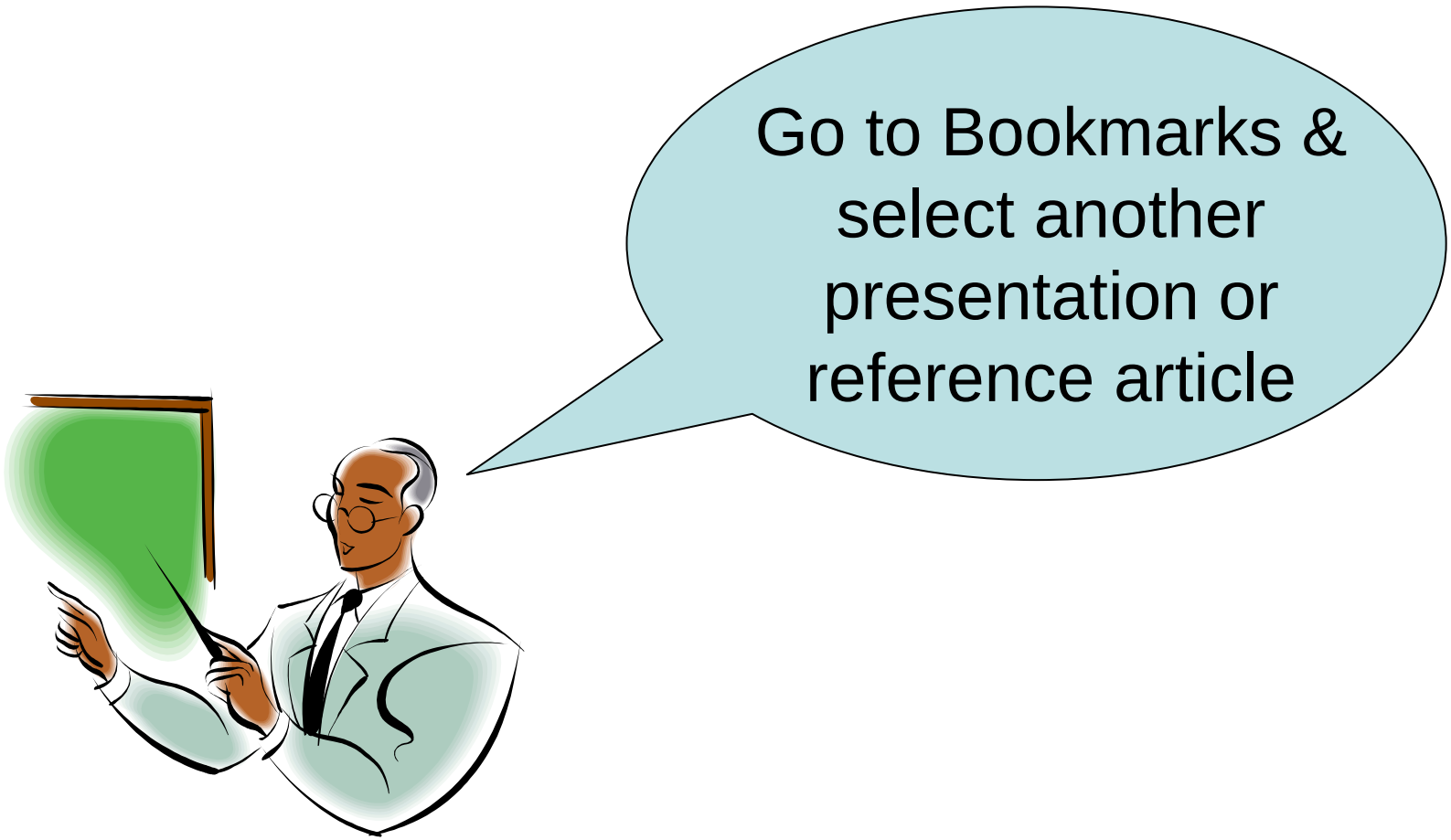
_____

_____

_____

Reviewer's signature _____

End of Selection



References

Acknowledgment:

Linda Cox, MD FAAAAI, David R. Weldon, MD FAAAAI, David I. Bernstein, MD FAAAAI, Arline M. Gerard, RN, and Harold S. Nelson, MD FAAAAI and the American Academy of Allergy, Asthma, and Immunology's Immunotherapy & Diagnostics Committee for laying the groundwork for this training material through their CME course: "Optimizing the Safety of Immunotherapy Administration Outside of the Prescribing Allergist's Office" January 2006 (http://www.aaaai.org/members/cme_ce/immunotherapy/)

Supporting Documentation:

Evaluation of near-fatal reactions to allergen immunotherapy injections, Hetal S. Amin, Gary M. Liss and David I. Bernstein; J Allergy Clin Immunol, 2006;117:169-175. Permission for use of this reference is granted by Elsevier through Rightslink® service provided the audience of the material consist of students or employees of an academic or government institution that has a full-text subscription to this journal.

Allergen Immunotherapy, Jennifer L. Huggins, R. John Looney; Am Fam Physician 2004;70:689-96,703-4. Permission for use of this reference is granted by Mindy Cleary, AAFP IP Coordinator for the American Academy of Family Practice. {Illustration removed}

Allergen Immunotherapy, a practice parameter second update, Linda Cox, James Li, Harold Nelson, Richard Lockey; J Allergy Clin Immunol, 2007;120:S25-85. Permission for use of this reference is granted by Elsevier through Rightslink® service provided the audience of the material consist of students or employees of an academic or government institution that has a full-text subscription to this journal.

Anaphylaxis:

Systemic Anaphylaxis, Alexandra Worobec, Dean Metcalf; Current therapy in allergy, immunology, and rheumatology 5th ed. 1996 St Louis: Mosby-Yearbook: pp 170-177. Permission for use of this reference is granted by Marek Gorczyca, Rights Assistant for Elsevier LTD. {fee paid}.

The diagnosis and management of anaphylaxis: An updated practice parameter, Phillip Lieberman, Stephen F. Kemp, John Oppenheimer, David M. Lang, I. Leonard Bernstein, Richard A. Nicklas; J Allergy Clin Immunol 2005;115(3):S483-523. Permission for use of this reference is granted by Elsevier through Rightslink® service provided the audience of the material consist of students or employees of an academic or government institution that has a full-text subscription to this journal.

End of Selection