

Consultation and referral guidelines citing the evidence: How the allergist-immunologist can help

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PREFACE

Allergic diseases affect at least 20% of the population, which means that at least 56,284,381 Americans have allergic diseases. Although there are currently only 5400 board-certified allergist-immunologists in this country, their expertise and services are often underused. We believe a major part of this underuse is a result of physicians and patients not really knowing what allergist-immunologists do and how we can help. It is the main purpose of these guidelines to define both the expertise of the allergist-immunologist and under what circumstances they can be of added value in the treatment of patients.

These guidelines started as a presidential initiative designed to help the American Academy of Allergy, Asthma and Immunology (AAAAI) fulfill its mission of “the advancement of the knowledge and practice of allergy, asthma, and immunology for optimal patient care.” The guidelines were subsequently developed as summarized in Fig 1, with the input of many AAAAI committees and individuals who are acknowledged in this supplement. The guidelines were reviewed and approved by the AAAAI leadership and presented to the AAAAI membership for comments before being finalized. The guidelines will be regularly updated on our Web site (www.aaaaai.org).

When one speaks of “referral,” there may be “business” or “turf” connotations. In an attempt to transcend such considerations, we based the consultation and referral guidelines on evidence that allergist-immunologist care improves patient outcomes. As described in the “Introduction,” this was either direct evidence that outcomes

improved with allergist-immunologist care or evidence that diagnostic or therapeutic interventions performed by allergist-immunologists improved outcomes. Because there has been a paucity of controlled intervention trials addressing this issue, the evidence is often observational. Moreover, some of the rationale statements are only supported by consensus or expert opinion. Nonetheless, we believe that trying to provide a rationale for each guideline and citing the best available evidence is a step forward in creating rational, useful, and evidence-based guidelines for consultation and referral. We look forward to future studies that would increase the evidence base for such guidelines.

The title *Consultation and referral guidelines* sends another important message. Although some patients will require ongoing allergist-immunologist management, others might require just a single or a limited number of consultations. Still others might benefit from coordinated primary care and allergist-immunologist follow-up (co-management). We hope these guidelines will allow the allergist-immunologist to function optimally as a member of the health care team for the ultimate benefit of the patients we serve.

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Disclosure of potential conflict of interest: M. Schatz has received grants from GlaxoSmithKline and Sanofi-Aventis and is on the speakers' bureau for AstraZeneca and Merck. D. Leung—none disclosed.

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J Allergy Clin Immunol 2006;117:S495-523.
0091-6749/\$32.00

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doi:10.1016/j.jaci.2005.10.047

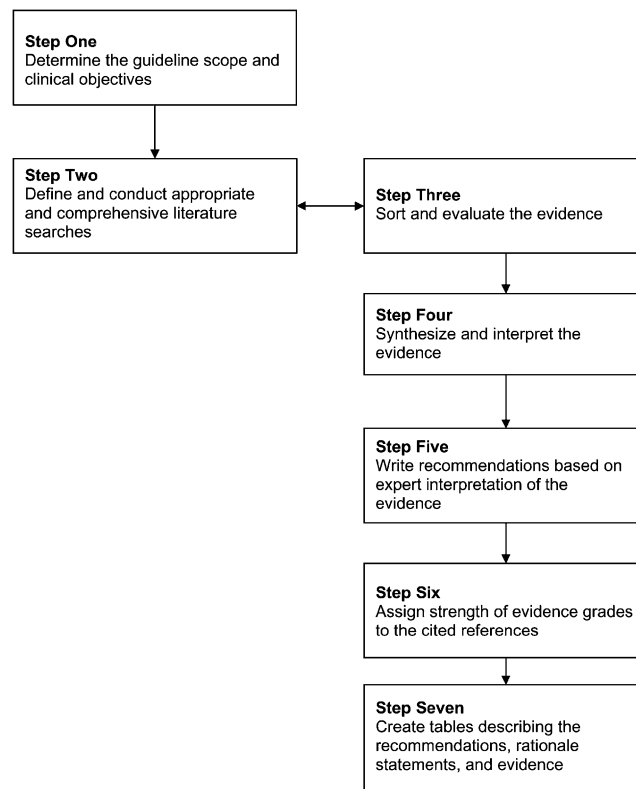


FIG 1. A summary of the development of the *Consultation and referral guidelines citing the evidence*.

INTRODUCTION

Allergic diseases affect more than 20% of the US population and are the sixth leading cause of chronic disease in the United States.¹ Allergic rhinitis alone leads to approximately 16.7 million office visits to health care providers each year,² and asthma causes nearly 2 million emergency department visits and 465,000 hospitalizations each year.³ Indirect costs from asthma are reported to be more than \$4.6 billion.⁴

Allergies and asthma cause unnecessary deaths each year: about 100 persons in the United States die from food-related anaphylaxis,⁵ and another 40 die from insect sting-induced anaphylaxis.⁶ Asthma leads to about 4300 deaths each year.⁴ For many patients with asthma and allergic diseases, working with an allergist-immunologist can assist them in managing their disease and preventing morbidity and mortality.

What is an allergist-immunologist?

An allergist-immunologist is a physician who has been trained in either internal medicine or pediatrics and who has completed an additional 2 (or more) years of training in allergy and immunology at an accredited training program. Most are certified in internal medicine, pediatrics, or both and have passed the examination given by the American Board of Allergy and Immunology.

The allergist-immunologist is uniquely trained⁷ in the following:

- allergy testing (skin test, *in vitro* studies);
- history-allergy test evaluation;
- bronchoprovocation testing (eg, exercise and methacholine);
- environmental control instructions;
- inhalant immunotherapy;
- immunomodulator therapy (eg, anti-IgE, intravenous immunoglobulin);
- venom immunotherapy;
- food and drug challenges;
- drug desensitization;
- evaluation of immune competence;
- education (disease, medications, and monitoring); and
- management of chronic or recurrent conditions in which allergy is not always identified: rhinosinusitis, conjunctivitis, asthma, cough, urticaria-angioedema, eczema, anaphylaxis.

How the allergist-immunologist can help

This *Consultation and referral guideline* developed by the American Academy of Allergy Asthma and Immunology is designed to assist patients and health care professionals in determining when referral to an allergist-immunologist could be helpful. This referral might be a single or limited

consultation, lead to co-management between a primary care provider and an allergist-immunologist, or require ongoing specialty care by the allergist-immunologist.

Providing information based on evidence to assist patients and health care providers in the decision-making process should benefit not only the individuals but our health care system as a whole. The evidence included in this guide is based on the following:

- diagnostic evidence: tests performed or interpreted by allergist-immunologists facilitate diagnosis;
- direct outcome evidence: evidence that intervention by an allergist-immunologist improves outcomes; and
- indirect outcome evidence: evidence that interventions performed by allergist-immunologists improve outcomes (evidence to support established pharmacologic management will generally not be reviewed).

The evidence cited for each allergic disease category is also graded according to the following system:

- Ia. Meta-analysis of randomized controlled trials
- Ib. Randomized controlled trial
- II. Nonrandomized, controlled intervention study
- III. Observational cohort or case-control study
- IV. Review article, expert opinion.

This document includes specific referral guidelines for 14 categories of allergic diseases, along with the rationale for the referral, references, and the type and grade of evidence provided (Tables I-XIV). The tables are presented alphabetically for easy navigation and do not refer to the prevalence of the individual disease. This information will be regularly updated on the AAAAI Web site (<http://www.aaaai.org/professionals/resources/rgce/>).

Guide to the tables

1. Allergic bronchopulmonary aspergillosis
2. Anaphylaxis (systemic allergic reaction)
3. Asthma
 - A. Asthma diagnosis
 - B. Environmental diagnosis and management
 - C. Asthma treatment: immunotherapy
 - D. Asthma treatment: prevention of morbidity
 - E. Asthma treatment: prevention of mortality
 - F. Asthma treatment: adherence
 - G. Occupational asthma

4. Conjunctivitis
5. Cough
6. Dermatitis
 - A. Atopic
 - B. Contact
7. Drug allergy
8. Food allergy
9. Hypersensitivity pneumonitis
10. Insect hypersensitivity
11. Occupational allergic diseases
12. Primary immune deficiency
13. Rhinitis-rhinosinusitis
 - A. Rhinitis
 - B. Sinusitis
14. Urticaria-angioedema

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TABLE I. Allergic bronchopulmonary aspergillosis

| Referral guideline | Rationale | Evidence type |
|--|---|------------------------------------|
| Patients with suspected or proven asthma or cystic fibrosis who have pulmonary infiltrates and peripheral blood eosinophilia | Allergen skin testing and <i>in vitro</i> tests, when correlated with history and other findings, can establish the diagnosis of ABPA. ¹ | Diagnostic |
| Patients with known ABPA for management | Allergist-immunologists are specifically trained to manage this disease, ² and outcomes of such management have been reported by allergist-immunologists. ³⁻⁵ | Indirect outcome (ABPA management) |

ABPA, Allergic bronchopulmonary aspergillosis.

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TABLE II. Anaphylaxis (see also "Drug allergy" [Table VII], "Food allergy" [Table VIII], and "Insect hypersensitivity" [Table X] for anaphylaxis caused by these agents)

| Referral guideline | Rationale | Evidence type |
|--|--|--|
| Individuals with a severe allergic reaction (anaphylaxis) without an obvious or previously defined trigger | After a severe allergic reaction without a known cause, a trigger should be identified if at all possible. An allergist-immunologist is the most appropriate medical professional to perform this evaluation, ¹ which might include skin testing, <i>in vitro</i> tests, and challenges when indicated (including with exercise, see below). Major triggers for anaphylaxis are foods and food constituents, medications and biologic agents, latex, and insect stings. ²⁻⁶ Future avoidance of the identified triggers should prevent subsequent anaphylactic episodes. | Diagnostic Indirect outcome (trigger avoidance) |
| | Management of idiopathic anaphylaxis by an allergist-immunologist is associated with a reduction in hospitalizations and emergency department visits. ⁷ | Direct outcome (idiopathic anaphylaxis) |
| Persons with anaphylaxis attributed to food | Food allergy is the most common cause of anaphylaxis outside of the hospital setting. ^{2,3,5} Allergist-immunologists use diagnostic modalities to confirm the trigger and use their specific training ¹ and clinical experience to educate patients regarding avoidance and immediate management to prevent potentially deadly outcomes. ⁸ | Diagnostic Indirect outcome (food avoidance, early interventions) |
| Exercise-induced anaphylaxis and food-dependent exercise-induced anaphylaxis | After an anaphylactic reaction that appears to have a significant relationship to exercise, it is crucial to be certain whether exercise is the cause and to determine whether a food might be involved. ⁹⁻¹² | Diagnostic Indirect outcome (avoidance) |
| Drug-induced anaphylaxis | Allergist-immunologists use diagnostic agents to confirm the drug responsible for the reaction, if these agents are available (see "Drug allergy" [Table VII]). | Diagnostic |

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TABLE III, A. Asthma diagnosis

| Referral guideline | Rationale | Evidence type |
|---|--|---|
| Patients with respiratory symptoms suggestive of asthma but with normal PFT results (FEV ₁ >80% of predicted value) and no significant reversibility (<12% and 200-mL increase in FEV ₁) | Allergists-immunologists perform methacholine challenges, which have a high sensitivity for current asthma. ^{1,2} | Diagnostic |
| Exercise-induced symptoms that are atypical or do not respond well to pretreatment with albuterol, nedocromil, or cromolyn | Further objective evaluation and confirmation with pulmonary function testing (including exercise challenge) in conjunction with appropriate allergist-immunologist evaluation will define diagnosis or differential diagnosis. ³ | Diagnostic |
| Subjects wishing to scuba dive with a history of asthma | There is a theoretic risk of increased barotraumas, as well as exercise-induced bronchospasm, in patients with asthma who scuba dive. Bronchoprovocation with exercise has been recommended to exclude asthma in scuba divers. ⁴ | Diagnostic Indirect outcome (scuba diving avoidance) |

PFT, Pulmonary function test.

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TABLE III, B. Asthma: environmental diagnosis and management

| Referral guideline | Rationale | Evidence type |
|--|--|--|
| Patients with a history of seasonal or persistent asthma for evaluation of inhalant sensitization to confirm the diagnosis | Exposure to indoor and outdoor allergens can worsen asthma. ¹⁻¹⁵ Allergy cannot be diagnosed on the basis of history alone. ¹⁶ Diagnosis is derived from correlation of clinical history and diagnostic tests, ¹⁶ with which allergist-immunologists are expert. ¹⁷ | Diagnostic |
| Patients who need management and education concerning environmental triggers | Allergists have familiarity with the wide variety of both indoor and outdoor aeroallergen exposures that have been shown to affect asthma and respiratory function. ¹⁷ Allergists are specifically trained to provide education regarding appropriate avoidance measures. ¹⁷ Allergen avoidance can improve asthma. ¹⁸⁻³⁰ | Indirect outcome (avoidance) |
| Patients with asthma who experience a worsening of symptoms after a new pet has been introduced into the home | Exposure to furred pets in allergic patients can worsen asthma symptoms. ^{31,32} Avoidance of pets in allergic patients can improve asthma symptoms, ³³ reduce airway responsiveness, ³⁴ and reduce the need for inhaled corticosteroids. ³⁴ | Diagnostic Indirect outcome (avoidance) |

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TABLE III, C. Asthma treatment: immunotherapy

| Referral guideline | Rationale | Evidence type |
|---|---|----------------------------------|
| Consider referral for allergen immunotherapy for asthmatic patients if there is a clear relationship between asthma and exposure to an unavoidable aeroallergen to which specific IgE antibodies have been demonstrated and the following: <ul style="list-style-type: none"> • poor response to pharmacotherapy or avoidance measures; • unacceptable side effects of medications; • desire to avoid long-term pharmacotherapy; • coexisting allergic rhinitis; and • long duration of symptoms (perennial or major portion of the year). | The efficacy of allergen immunotherapy in the treatment of allergic asthma has been demonstrated in many double-blind, placebo-controlled studies to multiple allergens (eg, pollen, animal allergen, fungi, and dust mite). ¹⁻⁴ | Indirect outcome (immunotherapy) |
| Consider referral for children with allergic rhinitis because immunotherapy can potentially prevent the development of asthma | One study suggests that allergen immunotherapy has been shown to reduce the development of asthma in children with allergic rhinitis compared with a group of children treated with medication alone. ⁵ Immunotherapy might also prevent the development of new allergen sensitivities. ⁶⁻⁸ | Indirect outcome (immunotherapy) |

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TABLE III, D. Asthma treatment: prevention of morbidity

| Referral guideline | Rationale | Evidence type |
|--|--|---|
| Patients with asthma who require emergency department care for an acute episode | Allergist care reduces subsequent asthma emergency department visits. ¹⁻¹¹ Allergist care reduces subsequent hospitalization. ²⁻¹¹ | Direct outcome |
| Patients with uncontrolled asthma | Allergist care reduces asthma symptoms and improves physical functioning and asthma-related quality of life. ^{1,3,11,12} | Direct outcome |
| Patients with persistent asthma, particularly moderate-to-severe persistent asthma | Inhaled corticosteroid use leads to reduction in asthma symptoms, exacerbations, hospitalizations, and asthma death. ¹⁰ Allergist care is more likely to lead to use of asthma controller medications (particularly inhaled corticosteroids). ^{5,7,10,12-15} Allergists administer anti-IgE, which prevents exacerbations, improves symptoms, and reduces the use of inhaled steroids in patients with moderate-to-severe asthma. ^{16,17} | Indirect outcome (controllers) Indirect outcome (anti-IgE) |

TABLE III, D. Asthma treatment: prevention of morbidity (continued)

| Referral guideline | Rationale | Evidence type |
|--|--|--|
| Patients who need education on asthma and guidance in techniques for self-management | Use of written action plans improves asthma self-management. ^{3,14,15} Allergist care is more likely to lead to provision of a written management plan and objective monitoring of asthma with peak flow meters. ^{3,14,15} Asthma self-management education improves outcomes in children and adults. ^{18,19} Allergist care is associated with more effective self-management education and knowledge. ^{3,11,20,21} | Indirect outcome (education, action plan) |
| Patients who use excessive amounts of reliever medications | Excessive short-acting β -agonist use indicates uncontrolled asthma. Allergist care reduces overuse of short-acting β -agonists. ¹⁴ | Direct outcome |
| Patients with severe asthma | Allergist care reduces cost of care for asthma. ^{6,8,9,22} | Direct outcome |

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TABLE III, E. Asthma treatment: prevention of mortality

| Referral guideline | Rationale | Evidence type |
|---|---|--|
| Patients with potentially fatal asthma (prior severe, life-threatening episode; prior intubation) | Improved pharmacologic therapy | |
| | Inhaled steroids have been associated with significant reductions in risk for fatal and near-fatal exacerbation of asthma. ¹ | Indirect outcome (inhaled and oral steroids) |
| | Allergist-immunologists prescribe inhaled steroids more frequently than primary care physicians, and patients seen and managed by allergist-immunologists are more likely to be taking inhaled steroids regularly. ²⁻⁶ | |
| | Oral steroid use for attacks reduces the risk of fatal asthma. ⁷⁻⁹ | |
| | Patients managed by allergist-immunologists are more likely to appropriately receive oral steroids. ^{6,10,11} | |
| | Immunologic therapy | |
| | Allergens can trigger severe and fatal asthma episodes. ¹² | Indirect outcome (avoidance, immunotherapy) |
| | Allergist-immunologists have expertise in performance and interpretation of skin tests for immediate hypersensitivity, education to encourage aeroallergen avoidance, and provision of inhalant allergen immunotherapy in properly selected patients. ¹³ | |
| | Allergen immunotherapy provides significant clinical benefit, ^{14,15} including for <i>Alternaria</i> species, ¹⁶ which has been associated with life-threatening asthma. ¹² | |
| | Anti-IgE therapy has been shown to improve outcomes in high-risk patients. ^{17,18} | |
| Objective monitoring of “poor perceivers” | | |
| A major factor contributing to risk for fatal asthma outcomes is underrecognition of asthma; some asthmatic patients are “poor perceivers.” ¹⁹ | Diagnostic | |
| Allergist-immunologists perform objective measurements of lung function more frequently than other physicians. ^{20,21} | | |
| Action plans | | |
| Action plans can reduce asthma mortality. ⁷ | Indirect outcome (action plans) | |
| Asthma specialists are more likely to provide action plans to their patients. ²² | | |

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TABLE III, F. Asthma treatment: adherence

| Referral guideline | Rationale | Evidence type |
|---|---|----------------|
| Patients with asthma in whom adherence problems might be limiting optimal control | <p>Patients with a visit to an allergist-immunologist in the prior year were significantly more likely to have been dispensed an optimally effective number of inhaled steroid canisters.¹</p> <p>Specialty care is associated with more refills of anti-inflammatory medications.²</p> <p>Patient compliance with national asthma guidelines was higher in patients of specialists.³</p> <p>Misunderstanding of asthma controller medications, which was associated with decreased adherence, was more likely in patients not treated by specialists.⁴</p> | Direct outcome |

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TABLE III, G. Occupational asthma

| Referral guideline | Rationale | Evidence type |
|---|--|---|
| Patients with a history suggesting occupational asthma should undergo testing to confirm the diagnosis of asthma and referral to an allergist for evaluation to establish that the asthma is caused by or triggered by agents at the workplace and to initiate appropriate avoidance therapy. | <p>History and physical examination are insufficient to confirm occupational asthma, and inaccurate conclusions can easily be drawn.^{1,2} Allergists can interpret spirometry when performed as a baseline, with response to bronchodilator, serial assessment of spirometry or peak flows, and changes in methacholine response during work periods versus off-work periods.³⁻⁹</p> <p>Allergists can outline the algorithm for the clinical investigation of suspected occupational asthma and interpret other studies to confirm bronchial hyperresponsiveness, including challenges with methacholine, histamine, cold air, or exercise, yet realize that such study results might be negative if performed when the patient is off work and free of symptoms.^{5,8}</p> | Diagnostic Indirect outcome (avoidance) |

TABLE III, G. Occupational asthma (*continued*)

| Referral guideline | Rationale | Evidence type |
|---|--|------------------------------|
| Consider referral of a worker with asthma for evaluation of workplace exposures that could worsen or exacerbate the asthma. | <p>Allergists can review Material Safety Data Sheets and other specific details of the workplace obtained either through specific questioning, direct observation during an onsite work evaluation, or assistance in obtaining an industrial hygiene survey in an effort to identify exposure to possible causal agents. Allergists can arrange and interpret workplace challenges and be able to provide assistance in referring to centers that can perform specific agent laboratory challenges if indicated.^{3,5,7}</p> <p>The importance of identifying the agent responsible for asthma is that continued exposure can lead to worsening asthma and possibly persistent disease, even after exposure ceases. Early accurate diagnosis and removal from further exposure to specific work sensitizers carries the best medical prognosis for those with occupational lung disease.¹⁰⁻¹⁶</p> | Indirect outcome (avoidance) |

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TABLE IV. Conjunctivitis

| Referral guideline | Rationale | Evidence type |
|---|--|---|
| Patients with prolonged or recurrent manifestations of allergic conjunctivitis Patients with comorbid conditions (eg, asthma, rhinitis, recurrent sinusitis) | Allergy cannot be diagnosed on the basis of history alone. ¹ Diagnosis is derived from a correlation of clinical history and diagnostic tests, with which allergist-immunologists are experienced. ² Allergists can help to suspect and diagnose corneal involvement in vernal and atopic keratoconjunctivitis. ^{3,4} | Diagnostic |
| Patients with symptoms interfering with quality of life, ability to function, or both Patients who have found medications to be ineffective or have had adverse reactions to previously prescribed medications | A thorough allergy evaluation will complement the patient history and aid in the development of specific treatment plans, including immunotherapy and environmental controls. These treatments can benefit patients with allergic conjunctivitis in terms of reduced symptoms, medication use, and cost. Allergen immunotherapy can be highly effective in controlling the symptoms of allergic conjunctivitis. ⁵⁻⁷ Efficacy parameters include symptom and medication scores, conjunctival challenge, and immunologic cell markers and cytokine profiles. Allergen immunotherapy can provide lasting benefits after immunotherapy is discontinued. ⁸⁻¹⁰ | Indirect outcome (avoidance, immunotherapy) |

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TABLE V. Cough

| Referral guideline | Rationale | Evidence type |
|---|---|--|
| Patients with chronic cough of 3-8 weeks or more | Asthma, postnasal drainage, and gastroesophageal reflux disease are the most common causes of cough. ^{1,2} Spirometry and a chest radiograph have been suggested as the minimum investigations required in the evaluation of chronic cough. ²⁻⁴ Allergists have extensive training to evaluate the upper, as well as lower, airways in a patient with chronic cough. ⁵ | Diagnostic |
| Patients with coexisting chronic cough and asthma | Cough occurs in all asthmatic subjects. ¹ However, cough alone is a poor marker of asthma, and asthma might be overdiagnosed in children with cough alone. ³ The allergist can both provide expert consultation to ensure the diagnosis of asthma is correct and to maximize therapy in the asthmatic subject (see "Asthma" [Tables III, A, through III, G]). | Diagnostic Indirect outcome (avoidance, pharmacologic, and immunologic therapy) |

TABLE V. Cough (*continued*)

| Referral guideline | Rationale | Evidence type |
|---|---|---|
| Patients with coexisting chronic cough and rhinitis | Postnasal drip is the single most common cause of chronic cough. ¹ Allergy skin testing and history-testing correlation can differentiate allergic from nonallergic rhinitis (see “Rhinitis” [Table XIII, A]). Treatment of rhinitis can improve the cough. ¹ Treatment of rhinitis by allergists improves patient outcomes (see “Rhinitis” [Table XIII, A]). | Diagnostic Indirect outcome (avoidance, pharmacologic, and immunologic therapy) |
| Patients with chronic cough and tobacco use or exposure | Tobacco smoke exposure clearly increases cough prevalence and exacerbates any pulmonary condition. ³ Chronic cough in cigarette smokers is dose related. ⁴ Allergists can assist with active steps to minimize or eliminate tobacco smoke exposure. ⁵ | Indirect outcome (smoking cessation) |

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TABLE VI, A. Atopic dermatitis

| Referral guideline | Rationale | Evidence type |
|--|--|--|
| To confirm the diagnosis of atopic dermatitis in a patient with dermatitis | Allergist-immunologists are specifically trained to diagnose atopic dermatitis. ¹ Defining IgE-mediated sensitivity (by means of skin or <i>in vitro</i> testing) is useful in the differential diagnosis. ² | Diagnostic |
| To identify the role of dust mite allergy in patients with atopic dermatitis | Dust mite allergy can trigger atopic dermatitis. In such patients mite avoidance should be helpful. ³⁻¹¹ | Diagnostic Indirect outcome (mite avoidance) |
| To identify the role of food allergy in patients with atopic dermatitis | Approximately 35% of young children with moderate-to-severe atopic dermatitis have food allergy; the association appears less common in adults but is possible. ¹²⁻¹⁹ | Diagnostic Indirect outcome (food avoidance) |
| Patients whose atopic dermatitis responds poorly to treatment | Allergist-immunologists are specifically trained and experienced in managing atopic dermatitis in both children and adults. ²⁰⁻²⁷ | Indirect outcome (pharmacologic therapy) |

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TABLE VI, B. Contact dermatitis

| Referral guideline | Rationale | Evidence type |
|--|---|---|
| To confirm the diagnosis of and identify the cause of contact dermatitis | Allergist-immunologists are specifically trained to diagnose contact dermatitis. ¹ More allergist-immunologists than dermatologists currently perform patch testing. ^{2,3} If a cause is defined, avoidance therapy can be initiated. ⁴⁻¹³ | Diagnostic Indirect outcome (avoidance) |

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TABLE VII. Drug allergy

| Referral guideline | Rationale | Evidence type |
|--|---|--|
| Patients with a history of penicillin allergy who have a significant probability of requiring future antibiotic therapy | The vast majority of patients with a history of penicillin allergy can safely use penicillins if an allergy evaluation, often including a penicillin skin test, is performed. ¹ | Diagnostic Indirect outcome (needed penicillin treatment) |
| | History alone is inadequate to rule out IgE-mediated allergy to penicillin. ² | |
| | Penicillin skin testing in advance of need does not cause significant re-sensitization. ³⁻⁶ | |
| | Patients who are shown not to be allergic to penicillin might be able to use more appropriate and potentially less toxic antibiotics, less expensive antibiotics, or both. ⁷ | |
| Patients with a history of penicillin allergy in which a penicillin-class antibiotic is the drug of choice | Skin test responses might be negative in such patients, who can then safely receive penicillin. ⁴ Antibiotic desensitization in patients with positive skin test responses renders them transiently tolerant and induces negative skin test responses, indicating blocking of mast cell-IgE activation events. ⁸⁻¹¹ | Indirect outcome (needed penicillin treatment) |
| Patients with histories of multiple drug allergy-intolerance | Allergist-immunologists provide a comprehensive plan to evaluate the historical adverse drug reactions and provide suggestions on future therapies to minimize risks. ¹²⁻¹⁷ | Diagnostic Indirect outcome (treatment with needed medications) |
| Patients who might be allergic to protein-based biotherapeutics and require use of these materials | Allergist-immunologists perform skin testing with appropriate concentrations and techniques to determine current sensitivity. ^{12,16-20} For example, insulin desensitization allows for continued insulin therapy in patients with prior systemic reactions. ^{21,22} | Diagnostic Indirect outcome (treatment with needed biotherapeutics) |
| Patients with histories of adverse reactions to NSAIDs who require aspirin or other NSAIDs | Allergist-immunologists accurately diagnose NSAID sensitivity through challenge testing. ²³ | Diagnostic |
| | Allergist-immunologists perform aspirin desensitization in patients with documented aspirin sensitivity who require aspirin for other medical conditions. ^{10,23} | Indirect outcome (needed NSAID treatment) |
| | Desensitization in patients with aspirin-exacerbated respiratory disease can improve the control of both upper and lower respiratory tract disease in these patients. ^{10,23,24} | Indirect outcome (improved respiratory symptoms) |
| Patients who require chemotherapy medication for cancer or other severe conditions and have experienced a prior hypersensitivity reaction to those medications | Desensitization allows for transient tolerance to chemotherapy medications when there is no alternative treatment. ²⁵⁻²⁷ | Indirect outcome (needed chemotherapy) |
| Patients with a history of possible allergic reactions to local anesthetics | Allergist-immunologists are able to perform skin testing and graded challenge to find a safe local anesthetic for future use. Virtually all patients with histories of reactions to local anesthetics can subsequently tolerate the same or an alternate agent. ²⁸⁻³⁰ | Indirect outcome (needed local anesthetic treatment) |
| HIV-infected patients with a history of adverse reactions to TM-S who need this therapy | Graded TM-S challenges can identify patients who are not currently sensitive to the drug and allow patients with reactions during challenge to subsequently tolerate the drug and safely continue therapy. ³¹⁻³⁷ | Diagnostic Indirect outcome (needed TM-S therapy) |
| Patients with a history of reactions to induction agents or to nonpenicillin antibiotics | Allergist-immunologists provide a comprehensive plan to evaluate the historical adverse drug reactions and provide suggestions on future therapies to minimize risks. ¹²⁻¹⁷ | Diagnostic Indirect outcome (treatment with needed medications) |

NSAID, Nonsteroidal anti-inflammatory drug; TM-S, trimethoprim-sulfamethoxazole.

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TABLE VIII. Food allergy

| Referral guideline | Rationale | Evidence type |
|--|--|---|
| Persons who have limited their diet on the basis of perceived adverse reactions to foods or additives | After allergy evaluation, an estimated one third of perceived adverse reactions to foods and a small fraction of adverse reactions to additives are verified. ¹⁻⁶ Evaluation by an allergist-immunologist is likely to result in an individual's ability to liberalize his or her diet (thereby likely improving nutrition and quality of life). | Indirect outcome (avoiding unnecessary diet restriction) |
| Persons with a diagnosed food allergy | The allergist-immunologist can apply and interpret diagnostic tests (skin prick tests, serum food-specific IgE assays, and oral food challenges) and advise patients on dietary avoidance and emergency care measures. ^{2,5,7,8} These are important aspects of care because (1) many allergies are not permanent and should be monitored for resolution, ² and (2) avoidance of allergenic foods and action taken in the event of exposure are difficult to undertake, are prone to errors, and can be dangerous, thus mandating proper education. ^{9,10} | Diagnostic Indirect outcome (food avoidance, early pharmacologic treatment of reaction) |
| Atopic families with or expecting a newborn who are interested in identifying risks for and preventing allergy | Family history is the strongest predictor of allergy. A sibling born to a family who already has a child with peanut allergy has a risk for that allergy that is more than 10 times greater than that of the general population. ¹¹ Specific guidelines are in place to approach potential allergy in a food allergy-prone child (eg, breast-feeding and avoidance of allergenic foods). ^{12,13} Meta-analyses of studies shows breast-feeding and avoidance of cow's milk-soy in the first year might reduce the risk for allergic disease. ^{14,15} The allergist-immunologist can evaluate the risks and explain possible approaches. | Diagnostic Indirect outcome (prevention of sensitization) |
| Persons who have experienced allergic symptoms (urticaria, angioedema, itch, wheezing, and gastrointestinal responses) in association with food exposure | The allergist-immunologist can perform diagnostic tests, such as skin tests, serum IgE tests, and oral food challenges to determine the cause of the reaction. ^{2,7,8,16} | Diagnostic Indirect outcome (food avoidance) |
| Persons who experience an itchy mouth from raw fruits and vegetables | These symptoms are typical of pollen-food allergy syndrome, or oral allergy syndrome, which can sometimes progress to or overlap with more severe allergic reactions. ¹⁷⁻¹⁹ The allergist-immunologist evaluates the reactions to determine the cause and to advise which foods to avoid, identify other potential problematic foods, and assess risks for a severe reaction. | Diagnostic Indirect outcome (food avoidance) |
| Infants with recalcitrant gastroesophageal reflux or older individuals with recalcitrant reflux symptoms, particularly if they experience dysphagia | Food allergy might be a cause of infantile reflux, and evidence of food responsiveness is high (about 40%) for children in whom symptoms do not respond well to standard therapies. ²⁰ Older individuals might have reflux symptoms and possibly dysphagia caused by eosinophilic esophagitis, a disorder that is also commonly food responsive. ^{21,22} | Diagnostic Indirect outcome (food avoidance) |
| Infants with gastrointestinal symptoms, including vomiting, diarrhea (particularly with blood), poor growth, and/or malabsorption, whose symptoms are otherwise unexplained, not responsive to medical management, and/or possibly food responsive (even if screening allergy test results are negative) | There are a group of food-responsive gastrointestinal disorders of infancy (including food protein-induced enteropathy, enterocolitis, and proctocolitis) that can be diagnosed, treated, and monitored with modalities with which allergist-immunologists are expert, including elimination diets and oral food challenges. ^{7,23-26} Most of the disorders affecting infants cannot be identified with simple screening tests. ²³⁻²⁶ | Diagnostic Indirect outcome (food avoidance) |
| Persons with known eosinophilic inflammation of the gut | Eosinophilic gastroenteritis, esophagitis, and/or gastroenterocolitis might be food responsive. ^{21,22} Patients' symptoms could improve after identification and elimination of causal foods, ²² modalities for which the allergist-immunologist is expert. | Diagnostic Indirect outcome (food avoidance) |

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TABLE IX. Hypersensitivity pneumonitis

| Referral guideline | Rationale | Evidence type |
|---|---|---|
| Early referral of patients with suspected hypersensitivity pneumonia to avoid continued environmental exposure resulting in permanent lung injury | Early accurate diagnosis and removal from further exposure to specific sensitizers carries the best medical prognosis for those with HP. ¹⁻⁴ Allergists are trained and experienced in environmental exposure history, physical examination, and clinical and laboratory diagnosis of HP. ⁵ | Diagnostic Indirect outcome (avoidance) |
| Diagnostic consultation in patients found to have NSIP | Histologic diagnosis of HP varies from the acute stage, subacute stage, and chronic form. Findings of NSIP should initiate the diagnostic consideration of HP because avoidance of the offending antigen and pharmacologic therapy might result in resolution of the disease or stop the progression of disease. ⁶ | Diagnostic Indirect outcome (avoidance and corticosteroids) |
| Patients with known HP for management | Allergist-immunologists are specifically trained to evaluate environmental exposures, evaluate immunologic results, and treat and follow HP, including oral corticosteroid treatment. ^{5,7-12} | Indirect outcome (avoidance and corticosteroids) |

HP, Hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia.

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TABLE X. Insect hypersensitivity

| Referral guideline | Rationale | Evidence type |
|--|--|--|
| Consider referral of patients with systemic reactions suspected or possibly caused by insect stings for accurate identification of specific allergen and consideration for venom immunotherapy (or whole-body extract in case of fire ant) | Up to 3% of the population is at risk for anaphylaxis to insect stings, with approximately 40 documented deaths annually. ¹⁻⁸ | Diagnostic Indirect outcome (avoidance, early pharmacologic treatment of reaction, immunotherapy) |
| | Patient identification of the specific insect species causing an allergic reaction is frequently incorrect. | |
| | Allergy testing and history-test correlation can more accurately identify specific insects responsible for an allergic reaction and can be helpful in diagnosis, treatment, and avoidance recommendations. ^{7,9-18} | |
| Consider referral of patients with systemic reactions suspected or possibly caused by biting insects for accurate identification of specific allergen | Skin testing is generally preferred over <i>in vitro</i> testing for the initial evaluation of venom-specific IgE antibodies. ^{4,5,13,15,17-21} | Diagnostic Indirect outcome (avoidance, appropriate pharmacologic therapy) |
| | Venom immunotherapy (or fire ant whole-body extract) greatly reduces the risk of systemic reactions in stinging insect-sensitive patients. ^{2,3,5,8,15,22-24} | |
| | Venom immunotherapy can prevent death caused by subsequent stings in hypersensitive patients. ^{3,5,15,25} | |
| Consider referral of patients receiving venom (or fire ant whole-body extract) immunotherapy annually for review of interval history, tolerance of immunotherapy, need for repeat testing, and need for continued therapy | Biting insects, such as <i>Triatoma</i> species and mosquitoes, have been identified as a cause of systemic reactions. ²⁶⁻³⁰ | Indirect outcome (avoidance, early pharmacologic therapy, immunotherapy) |
| | RASTs and skin tests to <i>Triatoma</i> species salivary gland extracts and whole-body extracts of other biting insects have been used to identify antigen-specific IgE in sera of hypersensitive patients. ³¹⁻⁴⁰ | |
| | Patient education by an allergist-immunologist, including the cause of the allergy, specific avoidance measures, recognition and treatment of anaphylaxis, and management of local side effects, might reduce patient anxiety and potentially reduce morbidity from future bites. ²⁶⁻³⁰ | |
| Regular review of interval history, immunotherapy dosing schedule, and adverse events can contribute to reduced complications of treatment. ^{17,18} | Regular review might identify new comorbidities or medications that increase the risk of poor outcomes from natural stings or insect immunotherapy reactions. ^{17,18,41-44} | Indirect outcome (avoidance, early pharmacologic therapy, immunotherapy) |

TABLE X. Insect hypersensitivity (*continued*)

| Referral guideline | Rationale | Evidence type |
|--------------------|--|---------------|
| | Assessment of reactions to interval stings can be used to monitor the effectiveness of immunotherapy and might be cause for consideration of changes in dose and schedule. ^{17,18,45-48} | |
| | The interval between maintenance dose injections can be increased to 4-week intervals during the first year of immunotherapy and eventually to every 6-12 weeks in some patients. ^{17,18,48,49} | |
| | Many patients can safely discontinue venom immunotherapy after at least 3-5 years of treatment, although some patients might need to continue immunotherapy indefinitely. An allergist-immunologist with experience in treating patients with insect venom allergy is best suited to facilitate individualized patient decisions. ^{17,18,50-62} | |

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TABLE XI. Occupational allergic diseases

| Referral guideline | Rationale | Evidence type |
|---|--|---|
| Workers (1) who anticipate being exposed to an agent or agents to which they are at risk of allergy development or (2) who are presently being exposed to and are at risk for an allergic reaction to an agent, including rhinitis, conjunctivitis, asthma or eczema, should be referred to an allergist-immunologist for assessment to determine whether the worker might be susceptible to rhinitis, asthma, dermatitis, urticaria, or anaphylaxis from the exposure. An example is a worker who will be exposed to latex and has spina bifida, congenital urogenital tract abnormalities, or a worker with a past history suggestive of latex allergy. | Workers with congenital urogenital tract abnormalities, patients with spina bifida, health care workers, and rubber workers have a very high prevalence of latex allergy. ¹⁻⁵ Workers with an allergy who might not be able to prevent exposure or are prone to accidental exposure should be educated on self-treatment of asthma, rhinitis, urticaria, eczema, and anaphylaxis and have appropriate medications to use to control symptoms and signs. Specifically, if the patient has a history of anaphylaxis, prescribing and educating the patient on the proper use of an EpiPen or similar device for self-administration of epinephrine might be life saving. Allergist-immunologists are specifically trained to educate patients regarding self-treatment of such reactions. ⁶ | Diagnostic Indirect outcome (avoidance) |
| Workers in whom the cause of occupationally induced lung disease, including asthma or hypersensitivity pneumonitis, skin disease, or upper respiratory disease, such as rhinitis or conjunctivitis, is unable to be determined on the basis of history alone, or objective evidence is necessary to confirm cause and effect between exposure and disease. | Skin testing and RAST testing often can identify the cause of a hypersensitivity reaction. ⁷ Continued exposure to an allergen might result in progressive lung volume loss, which could be irreversible. ⁸ In most cases avoidance of the identified agent is the optimal treatment for occupational diseases. ⁹ Correlation of the history with the results of IgE testing helps prevent inappropriate avoidance, which might be suggested by RASTs alone. ^{10,11} In cases in which the cause cannot be isolated adequately on the basis of history, skin tests, or RASTs, inhalation challenge, which is the gold standard, can be arranged to provide objective evidence of a hypersensitivity reaction. ¹² | Diagnostic Indirect outcome (avoidance) |
| Workers with occupationally induced rhinoconjunctivitis | Workers with rhinoconjunctivitis are at an increased risk of asthma. Early avoidance might decrease the risk of further respiratory disease. ¹³ By means of history, skin tests, and/or RASTs and correlating the history and objective findings, the causative agent can often be identified, allowing appropriate avoidance and preventing possible loss of occupation or serious lung disease. ¹⁴ Prognosis of occupationally induced respiratory disease is dependent on the extent and duration of exposure. ¹⁵ | Diagnostic Indirect outcome (avoidance) |
| Referral to an allergist-immunologist for career counseling should be considered for adolescents with allergic disease who might be considering careers with exposure to animals or other allergens. | On the basis of history and relevant studies, allergist-immunologists can assess the future relative risks of such patients in the workplace. ^{7,16} These individuals can then be aware of any degree of increased risk of sensitization and be able to modify career plans with suitable advice. | Indirect outcome (avoidance) |
| Workers in occupations with animal exposure who experience rash, upper respiratory tract symptoms, eye symptoms, or lung symptoms | Upper respiratory and lower respiratory tract, skin, and eye symptoms might be due to allergic sensitization to the animals. Allergy testing can confirm sensitization and lead to appropriate interventions. ¹⁶ | Diagnostic Indirect outcome (avoidance) |
| Persons with occupational exposure to food proteins and chronic skin symptoms, respiratory symptoms, or both, attributable to the work environment | Occupational disease might be related to exposure to food proteins, such as wheat ("Baker's" asthma), or food handling (contact urticaria, contact dermatitis) that is diagnosed through modalities available to the allergist-immunologist. ⁷ Avoidance is the treatment of choice. ^{17,18} | Diagnostic Indirect outcome (avoidance) |

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TABLE XII. Primary immune deficiency

| Referral guideline | Rationale | Evidence type |
|---|--|--|
| Any of the following warning signs: <ul style="list-style-type: none"> • 8 or more new infections within 1 year; • 2 or more serious sinus infections within 1 year; • 2 or more months on antibiotics with little or no effect; • 2 or more pneumonias within 1 year; • failure of an infant to gain weight or grow normally; • recurrent deep skin or organ abscesses; • persistent thrush in the mouth or elsewhere on skin after age 1 year; • need for intravenous antibiotics to clear infections; • 2 or more deep-seated infections; • a family history of immune deficiency | Frequent infection, unusual infections, or unusual complications of usual infections are the most frequent presentation of immune deficiency. ¹⁻⁷ Advanced diagnostic strategies are necessary to ensure appropriate diagnosis and treatment. ^{1,6-8} Allergist-immunologists are trained to diagnose and treat primary immunodeficiency. ⁹ | Diagnostic |
| | Immunologic therapy improves immunity, ^{10,11} reduces infections, ¹²⁻¹⁴ improves organ function, ¹⁵ prevents complications, ¹ improves quality of life, ¹⁶ and might be curative ^{17,18} in patients with primary immune deficiencies. | Indirect outcome (immunologic therapy) |

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TABLE XIII, A. Rhinitis

| Referral guideline | Rationale | Evidence type |
|--|--|--|
| Patients with prolonged or severe manifestations of rhinitis with comorbid conditions (eg, asthma or recurrent sinusitis); with symptoms interfering with quality of life, ability to function, or both; or who have found medications to be ineffective or have had adverse reactions to medications ¹⁻³ | Allergist-immunologist care for rhinitis is associated with improved quality of life, compliance, and satisfaction with care. ^{4,5} | Direct outcome |
| | Allergy cannot be diagnosed on the basis of history alone. ⁶ Allergist-immunologists are highly trained to interpret the clinical history and allergy diagnostic test results in both upper and lower airway conditions. ⁷ | Diagnostic |
| | Allergist-immunologists have familiarity with the wide variety of both indoor and outdoor aeroallergen exposures that have been shown to affect the upper respiratory tree and have the expertise to provide avoidance education. ⁷ | Indirect outcome (avoidance) |
| | Allergen immunotherapy can be highly effective in controlling the symptoms of allergic rhinitis. ⁸ Allergen immunotherapy might provide lasting benefits after immunotherapy is discontinued. ⁹ | Indirect outcome (immunotherapy) |
| Patients with nasal polyps | Allergist-immunologists are specifically trained and experienced in the medical management of nasal polyps, including intranasal steroids, oral steroids, and treatment of complicating sinusitis ^{1,7} | Indirect outcome (pharmacologic therapy) |
| In addition to the above guidelines, consider referral of the child with allergic rhinitis because of the potential preventive role of allergen immunotherapy in progression of allergic disease. | Allergen immunotherapy has been shown to reduce development of new sensitizations and asthma in children with allergic rhinitis compared with children with allergic rhinitis treated with medication alone. ¹⁰ | Indirect outcome (immunotherapy) |

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TABLE XIII, B. Sinusitis

| Referral guideline | Rationale | Evidence type |
|--|---|--|
| Patients with chronic rhinosinusitis of any type | This set of conditions related to chronic inflammation of the sinus and contiguous nasal mucosa often coexists with allergic rhinitis. ¹ Allergist-immunologist care is associated with improved outcomes. ² | Direct outcome |
| | Allergy immunotherapy is demonstrated to improve outcomes in patients with concomitant allergic rhinitis. ³ | Indirect outcome (immunotherapy) |
| Patients with chronic or recurrent infectious rhinosinusitis | Many patients with this condition have humoral immunodeficiency, cystic fibrosis, fungal sinusitis, or granulomatous diseases. ¹ Allergist-immunologists are trained in the evaluation and management of these disorders. ⁴ | Diagnostic Indirect outcome (avoidance, pharmacologic, and immunologic therapy) |
| Patients with chronic eosinophilic rhinosinusitis | This is a chronic inflammatory disease with characteristics of allergic inflammation. ¹ It often coexists with aspirin sensitivity, asthma, and sinus-nasal polyposis. ^{5,6} Allergist-immunologists are experts in allergic inflammation and can evaluate and treat both environmental allergy and aspirin sensitivity. ⁴ | Diagnostic Indirect outcome (avoidance, pharmacologic, and immunologic therapy) |
| Patients with allergic fungal rhinosinusitis | This is a chronic inflammatory disease with characteristics of IgE and eosinophilic inflammatory response to fungi in sinuses. ^{7,8} Evaluation involves allergy skin testing and other laboratory testing. ⁹ Management involves medical management, allergen immunotherapy, and surgery. ^{9,10} Allergist-immunologists are experts in the evaluation and management of allergic diseases, including allergy immunotherapy. ⁴ | Diagnostic Indirect outcome (pharmacotherapy, immunotherapy) |

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TABLE XIV. Urticaria and angioedema (see also "Anaphylaxis" [Table II], "Drug allergy" [Table VII], and "Food allergy" [Table VIII])

| Referral guideline | Rationale | Evidence type |
|---|--|---|
| Patients with acute urticaria or angioedema without an obvious or previously defined trigger | After a severe allergic reaction without a known cause, a trigger should be identified, if at all possible. ¹ An allergist-immunologist is the most appropriate medical professional to perform this evaluation, ² which might include a detailed history, physical examination, skin testing, <i>in vitro</i> testing, and challenges when indicated. | Diagnostic |
| | Future avoidance of the identified triggers should prevent subsequent anaphylactic episodes. | Indirect outcome (avoidance) |
| Patients with acute urticaria or angioedema caused by a presumed food or drug with need for diagnostic confirmation or assistance with avoidance procedures | See "Food allergy" (Table VIII) and "Drug allergy" (Table VII) | Diagnostic Indirect outcome (avoidance) |
| Patients with chronic urticaria or angioedema (ie, those with lesions recurring persistently over a period of 6 weeks or more) | Allergists and dermatologists have more expertise in caring for patients with urticaria than other specialists. ³ Chronic urticaria often has an autoimmune pathogenesis. ⁴ Consultation with an allergist-immunologist would include (1) reviewing possible causative factors (medications, supplements, dietary factors, animal exposures, and physical factors), (2) possible skin testing, (3) possible physical challenges, (4) recommended changes in ingestants or contactants, and (5) optimal pharmacotherapy. ¹⁻⁸ Allergy-immunology specialists are also knowledgeable of the minimal benefit of multiple laboratory tests in urticaria with an otherwise normal examination. ¹⁻³ | Diagnostic Indirect outcome (avoidance, pharmacotherapy) |
| Patients who might have urticarial vasculitis or urticaria with systemic disease (vasculidities, connective tissue disease, rarely malignancies): a. Lesions last more than 24 hours; leave ecchymotic, purpuric, or hyperpigmented residua on or under the skin; or are associated with pain or burning b. Patients who have typical urticaria-angioedema but have signs and symptoms suggestive of systemic illness c. Patients whose symptom control requires regular steroid use | Allergist-immunologist training and expertise should allow appropriate differential diagnosis, determination of the need for biopsy, elimination of a specific inciting agent, and optimal pharmacotherapy. ^{2,5,9,10} | Diagnostic Indirect outcome (avoidance, pharmacotherapy) |
| Patients with chronically recurring angioedema without urticaria | Such patients might have hereditary or acquired angioedema, paraproteinemia, or B-cell malignancies. Allergist-immunologist expertise should allow optimal differential diagnosis, determination of the need for hematology-oncology evaluation, and pharmacologic therapy of hereditary or acquired angioedema caused by C1 esterase inhibitor deficiency. ¹¹⁻¹³ | Diagnostic Indirect outcome (pharmacotherapy) |
| Patients with suspected or proved cutaneous or systemic mastocytosis | Allergist-immunologists are trained to diagnose and treat this disease. ^{2,14-16} | Diagnostic Indirect outcome (pharmacotherapy) |

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