02.01.01 Allergy Immunotherapy

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This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

Related Policies:

- 02.02.02 Allergy Testing
- For information regarding sublingual immunotherapy (SLIT) see the following Pharmacy Policies
  - 05.01.109 Grastek
  - 05.01.110 Oralair
  - 05.01.111 Ragwitek
  - 05.02.31 Odactra
- For oral peanut immunotherapy see Pharmacy Policy:
  - 05.03.95 Palforzia

Summary

Description

Note: *This policy will address allergy immunotherapy and rapid desensitization, for Allergy Testing see medical policy 02.02.02. For information regarding sublingual immunotherapy (SLIT) see the following*

Pharmacy Policies: Grastek, Oralair, Odactra. and Ragwitek. For oral peanut immunotherapy see pharmacy policy: Palforzia.

Allergy immunotherapy is defined as the repeated administration of specific allergens to individuals with IgE-mediated conditions, for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.

Allergy immunotherapy (also known as desensitization, hyposensitization, allergy injection therapy, or "allergy shots"), is indicated in individuals whose triggering allergens are not readily avoidable, the allergy is IgE-mediated as documented by skin testing or RAST, the symptoms are not easily controlled with medication, the symptoms encompass more than one season, and the patients are likely to cooperate in the program.

Summary of Evidence

Allergy Immunotherapy – Subcutaneous

For individual's with IgE mediated allergies documented by skin testing or RAST whose triggering allergens are not readily avoidable or responsive to pharmacologic therapy subcutaneous allergy immunotherapy (SCIT) is utilized to prevent or lessen an allergic reaction as a second-line therapy, the evidence includes randomized controlled trials (RCTs). Relevant outcomes symptoms, quality of life (QOL), hospitalizations, medication use, and treatment-related morbidity. Most randomized controlled studies demonstrating efficacy with subcutaneous immunotherapy (SCIT) have been conducted with single-allergen extracts. Although some guidelines have recommended against the use of multiple allergen mixes in treatment, allergists in the United States commonly administer a mixture of multiple allergens to which the patient is sensitive with the rationale that effective immunotherapy should include all major sensitivities. In a review by Nelson et.al. (2009) three of the five studies demonstrated that multiallergen immunotherapy was effective. Outcomes related to the three effective studies found in D1 more children with asthma who received moderate-to-high doses of allergen (containing all of the inhalant allergens to which they were sensitive) were free of asthma after 4 years and on reaching age 16 years than were children with asthma who received placebo or very low doses of allergen; studies D2 and D3 with the complete removal of or 95% reduction in ragweed from multiallergen treatment resulted in the occurrence of significantly more symptoms the next pollen season. The latter finding clearly indicated that ragweed extract provided significant relief, despite its combination with multiple other extracts in the treatment program. In the two studies (D4 and D5) that did not show efficacy the limitations may have resulted in suboptimal outcomes may have been related to dose insufficiency or lack of treatment of key sensitivities. Findings from this review suggested that the simultaneous delivery of multiple unrelated allergens can be clinically effective with proper identification of relevant allergen and treatment with adequate doses is necessary for a sufficient period of time. However, there is a need for additional studies with more than 2 allergen extracts to assess safety and efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes. Therefore, even though there is paucity in the scientific evidence regarding the use of SCIT using multiple antigens, it is widely considered an established second-line treatment option in accordance with generally accepted standards of medical practice in the United States for documented IgE mediated allergies. Therefore, SCIT will be considered medically necessary when the criteria below is met, see Policy.

For individuals who have the following: food allergy, migraine headaches, vasomotor rhinitis, intrinsic (non-allergic) asthma, angioedema, atopic dermatitis and chronic urticaria currently there is paucity in the evidence in the peer reviewed medical literature as there were no studies identified that support SCIT is beneficial for these indications. Relevant outcomes symptoms, QOL, hospitalizations, medication use,

and treatment-related morbidity. In the guidelines from the National Institute of Allergy and Infectious Disease (NIAID) (Boyce et.al. 2010) states “immunotherapy for IgE mediated food allergies is not recommended, while this approach may show promise it is currently difficult to draw conclusions on the safety and whether clinical tolerance i.e., improvement in clinical symptoms that persists even after allergen specific immunotherapy is discontinued will develop with long-term treatment. Additional safety and efficacy data is needed before such treatment can be recommended.” Further studies are needed to determine safety and efficacy of SCIT for these indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Rapid Desensitization

For individuals with a IgE mediated drug hypersensitivity reaction to drugs (i.e., antibiotics, biologics, or chemotherapy agents), the evidence includes an evidence review to inform drug allergy practice parameters. Relevant outcomes symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. In the evidence review performed by Khan et. al. 2022 to inform drug allergy practice parameters they found that evidence for rapid drug desensitization which allows the patient with a drug hypersensitivity reaction to receive an uninterrupted course of the medication safely when they cannot be treated effectively with alternative medications, evidence was generally limited and of low certainty. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes. However, even though there is a paucity in the scientific evidence regarding rapid desensitization this treatment is widely considered to be in accordance with generally accepted standards of medical practice in the United States and will be considered medically necessary when the criteria below are met, see Policy.

For individuals with hypersensitivity to insect sting(s) (e.g., wasps, hornets, bees, fire ants) also known as Hymenoptera, the evidence includes a systematic review an updated consensus report. Relevant outcomes are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. Dhami et. al. in (2017) performed a systematic review and meta-analysis to assess allergy immunotherapy (AIT) effectiveness and safety in the management of insect venom allergy (venom immunotherapy [VIT]). It was noted there was paucity of high-quality evidence regarding VIT, however, effectiveness of VIT for individuals that experience moderate-to-severe systemic reactions to venom are likely to benefit from treatment with VIT either conventional AIT or rush protocols. In an updated consensus report by Burks et.al. 2013 from the American Academy of Allergy, Asthma and Immunology and European Academy of Allergy Clinical Immunology allergy immunotherapy (AIT) is an effective treatment for allergic asthma and rhinitis, as well as venom-induced anaphylaxis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes, However, even though there is a paucity in the scientific evidence regarding AIT for hypersensitivity to insect sting(s) this treatment is widely considered to be in accordance with generally accepted standards of medical practice in the United States and will be considered medically necessary when the criteria below are met, see Policy.

For individuals with moderate-to-severe allergic rhinitis (AR) including those individuals needing treatment during or immediately before the season of the affecting allergy requiring rapid desensitization, the evidence includes an evidence review to inform a practice parameter for rhinitis and a comparative observational study. Relevant outcomes are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. Dykewicz et. al. in (2020) performed an evidence review to inform the rhinitis practice parameter update in which allergy immunotherapy (AIT) may be offered through shared decision making to individuals with moderate-to-severe AR who are not controlled with allergen avoidance and/or pharmacotherapy. In 2015 Fan et. al. noted there is a limited number of studies that have compared the efficacy and safety of conventional immunotherapy with cluster immunotherapy in the treatment of moderate-to-severe AR, and completed a comparative observational study regarding cluster immunotherapy versus conventional immunotherapy in patients with AR. In this study they found “utilizing

the cluster immunotherapy protocol the maintenance dose was reached at 6 weeks, reducing the dose accumulation phase by >60% compared to conventional immunotherapy protocol." During the dose accumulation phase systemic adverse reactions occurred in 4 cases (13.79%) with six incidences (1.35%) in the conventional therapy group, and three cases (10.71%) with five incidences (1.27%) in the cluster immunotherapy group. The results of this study suggested that cluster immunotherapy is able to improve symptoms in patients with AR and "therefore, cluster immunotherapy may be a rapid, effective, safe treatment for moderate- to -severe persistent AR." The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes. However, even though there is a paucity in the scientific evidence regarding AIT rapid desensitization (cluster immunotherapy) related to moderate-to-severe allergic rhinitis (AR) this treatment is widely considered to be in accordance with generally accepted standards of medical practice in the United States and will be considered medically necessary when the criteria below are met, see Policy.

Aspirin Desensitization

For individuals who require rapid desensitization to aspirin and aspirin-type NSAIDs hypersensitivity, the evidence includes an evidence review to inform drug allergy practice parameters. Relevant outcomes include symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. In the evidence review by Khan et. al. (2022) regarding aspirin and aspirin-type NSAIDs hypersensitivity, the evidence found the utilization of a desensitization protocol was appropriate in the use of individuals with AERD that require aspirin or aspirin or aspirin-type NSAIDs for cardio protection, pain relief, or to control nasal polyp regrowth. This was based on a conditional recommendation and moderate level of evidence (see, Practice Guideline and Position Statements). The evidence is insufficient in determining this technology results in improved net health outcomes. However, even though there is a paucity in the scientific evidence regarding aspirin desensitization this treatment is widely considered to be in accordance with generally accepted standards of medical practice in the United States and will be considered medically necessary when the criteria below are met, see Policy.

Sublingual Immunotherapy for Food Allergy

For individuals who have food allergy who receive SLIT, the evidence includes RCTs, systematic reviews, and 2 interventional studies. Relevant outcomes are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. A few RCTs have evaluated SLIT for the treatment of food allergies, and these studies have had small sample sizes and tended to be rated as low quality by systematic reviewers. The available RCTs have not consistently found that SLIT is more effective than placebo or oral immunotherapy in individuals with non-peanut allergies; in individuals with peanut allergy, while available studies indicate efficacy of SLIT relative to placebo or pre-treatment baseline, SLIT has not been found to be as effective as oral immunotherapy. No RCTs were identified that compared SLIT with SCIT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Alternative Allergy Immunotherapy Treatments

For individuals whose triggering allergens are not readily avoidable there are numerous alternative allergy treatment methods which have been identified in the literature and are being researched. Relevant outcomes symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. These alternative allergy treatment methods remain unproven at this time due to a lack of supporting evidence published in the peer-reviewed scientific literature. The clinical utility of these techniques in the management of allergic disease have not yet been established. Some of the alternative allergy treatment methods utilize extracts that are not U.S. Food and Drug Administration (FDA)-approved. The evidence is insufficient in determining this technology results in improved net health outcomes.

OBJECTIVE

The object of this evidence review is to determine whether allergy immunotherapy (subcutaneous) and rapid desensitization improves the net health outcomes in individuals with IgE mediated allergies and individuals with hypersensitivities to drugs, venom from insect stings and need for immediate treatment for moderate-to-severe allergic rhinitis.

PRIOR APPROVAL

Not applicable.

POLICY

Allergy Immunotherapy (Subcutaneous)

Allergy immunotherapy (subcutaneous) may be considered **medically necessary** for the treatment of the following IgE-mediated allergies:

- Allergic (extrinsic) asthma
- Dust mite atopic dermatitis
- Hymenoptera (e.g., stinging insects; venom) sensitive individuals
- Mold-induced allergic rhinitis
- Perennial rhinitis
- Seasonal allergic rhinitis or conjunctivitis;

When the following conditions are met:

- The individual has severe, seasonal, or perennial IgE-dependent symptoms of allergic rhinoconjunctivitis or asthma after natural exposure to the allergen and both of the following criteria are met:
    - The individual has skin test and/or serological evidence of IgE-mediated antibody to a potent extract of the allergen; **and**
    - Avoidance or pharmacologic therapy cannot control allergic symptoms or member has unaccepted side effects with pharmacologic therapy; **or**
- The individual has a life-threatening IgE mediated allergy to insect stings (venom); **or**
- The individual has hypersensitivity to allergens that cannot be managed by medication or avoidance.

Allergy immunotherapy (subcutaneous) for the treatment of other indications including but not limited to the following is considered **investigational** because its effectiveness for indications other than the ones listed above has not been established:

- Angioedema
- Atopic dermatitis (except as indicated above)
- Chronic urticaria
- Food allergies,
- Intrinsic (non-allergic) asthma

- Migraine headaches
- Nasal polyposis
- Non-allergic vasomotor rhinitis

Rapid Desensitization

Rapid desensitization may be considered **medically necessary for** any of the following indications:

- Allergy to a particular drug that cannot be treated effectively with alternative medications; ***or***
- Insect sting (venom) hypersensitivity (Hymenoptera); ***or***
- Members with moderate to severe allergic rhinitis who need treatment during or immediately before the season of the affecting allergy.

Rapid desensitization is considered **investigational** for other indications because the evidence is insufficient in determining this technology results in improved net health outcomes.

Aspirin Desensitization

Aspirin desensitization may be considered **medically necessary** for aspirin sensitive individuals who require administration of aspirin (ASA) or Aspirin (ASA) – like drugs NSAIDs (aspirin avoidance is not possible) in the setting of the following:

- Chronic rhinosinusitis with nasal polyposis that is refractory to topical glucocorticoids, leukotriene modifying agents, and other therapies; ***or***
- Stable cardiovascular disease or cardiovascular risk factors requiring aspirin antiplatelet therapy; ***or***
- The need for NSAIDS to treat chronic inflammatory conditions, such as arthritis; *or*
- Antiphospholipid syndromes during pregnancy; ***or***
- Poorly controlled asthma.

Aspirin desensitization is considered **investigational** for other indications because the evidence is insufficient in determining this technology results in improved net health outcomes.

Notes:

- *Allergens should be individually prepared for the individual and the allergen content should be based on appropriate skin testing or appropriate in vitro testing.*
- *If a woman is contemplating pregnancy and requires initiation of allergy immunotherapy and/or it is anticipated that she will require allergy medications that may increase risk to her or the fetus, rapid desensitization is an acceptable approach.*

Alternative Allergy Immunotherapy Treatments

Alternative allergy Immunotherapy treatments including but not limited to the following are considered **investigational** because they have not been proven to be effective, the evidence is insufficient in determining the technology results in improved net health outcomes:

- Allergoids (modification of allergens to reduce allergenicity)
- Autogenous urine immunization (urine auto injection)
- Detoxification for allergies
- Epicutaneous immunotherapy (EPIT)
- Enzyme potentiated desensitization (EPD)

- Helminth Trichuris suis therapy for allergic rhinitis
- Homeopathic remedies for allergies
- Injection of food extracts
- Intranasal immunotherapy
- Low dose immunotherapy
- Multiple chemical sensitivity syndrome (environmental chemical avoidance for idiopathic environmental intolerances)
- Peptide therapy
- Provocation – neutralization therapy
- Rhinophototherapy
- Rotational and multiple food elimination diets (e.g., rotary diversified diet)
- Sublingual immunotherapy (SLIT) for food allergies

Non-Covered

Allergen-proof supplies, such as mattresses, pillows, and casings, etc., are considered personal convenience items and are therefore considered a **non-covered benefit**, refer to the member's plan document.

POLICY GUIDELINES

Required Documentation

The member's medical record must contain documentation that fully supports the medical necessity for services included within this medical policy. This documentation includes, but is not limited to, relevant medical history, physical examination and results of pertinent diagnostic tests or procedures.

- Include the following information:
    - Medical history, examination, and results of diagnostic testing (including allergy testing) upon which the need for the treatment is based.
    - Plan of treatment and dosage regimen must be documented in the member's medical record. The record should be prepared so that data regarding injection and responses can be appreciated in a logical and sequential sense.
    - When an evaluation and management service is billed on the same day as allergen immunotherapy (by the same physician) a separately identifiable service must be documented in the medical record.
    - Documentation must support the use of the code (e.g., number of venoms, number of vials).

Frequency Limits: Per Unit Reimbursement for Allergy Immunotherapy

Per unit reimbursement for allergy immunotherapy is based on the number of dosages prepared and intended for administration, and will be limited to following when the medical necessity criteria above are met:

Note: *Frequency limits are calendar year January-December*.

Code	Max Units
95115	1
95117	1
95120	0
95125	0
95130	0
95131	0
95132	0
95133	0
95134	0
95144	30
95145, 95146, 95147, 95148 and 95149	120 units (all codes combined) per calendar year (January-December)
95165	180 units per calendar year (January-December)
95170	10

Coding

See the Codes table for details.

BACKGROUND

The treatment of allergies is approached 3 ways: avoidance therapy, pharmacologic therapy, and immunotherapy. Complete avoidance of the known allergen responsible for inducing the signs and symptoms of the allergy is the most effective treatment for any allergic condition and results in a cure. When avoidance of a specific allergen such as house dust, molds or pollens is impossible, pharmacologic therapy is used (e.g., antihistamines, adrenergic agonists, anticholinergics, beta-adrenergic agonists, corticosteroids, cromolyn sodium and methylxanthines). It has been advocated that the utilization of air cleaners, humidifiers, or dehumidifiers is helpful in reducing allergic irritant substances

in the environment; however, research indicates that the use of these mechanical devices was ineffective in reducing clinical symptoms.

Allergy immunotherapy (also known as desensitization, hyposensitization, allergy injection therapy, or "allergy shots"), is indicated in individuals whose triggering allergens are not readily avoidable, the allergy is IgE-mediated as documented by skin testing or RAST, the symptoms are not easily controlled with medication, the symptoms encompass more than one season, and the individuals are likely to cooperate in the program. The severity, duration and frequency of episodes should be explored. Individuals with life-threatening allergy (severe anaphylactic reaction) to Hymenoptera (venom from bees, hornets, wasps or fire ants) have been shown to respond well to allergy immunotherapy, as well as individuals with severe seasonal allergic rhinitis or conjunctivitis, perennial allergic rhinitis, allergic (extrinsic) asthma and mold induced allergic rhinitis. Allergy immunotherapy will help desensitize the individual to the effects of the allergen. The documented allergy should correspond to the allergen planned for immunotherapy. A trial of systemic medications or avoidance of the allergens should be attempted. Two or more medications (antihistamines, steroids, bronchodilators, intranasal cromolyn) if not contraindicated should have been prescribed during the past year or the individual should be currently receiving immunotherapy.

Allergy immunotherapy is defined as the repeated administration of specific allergens to individuals with IgE-mediated conditions, for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens. The exact mechanism of action is not known but may involve an increase in allergen-specific IgG antibodies, a decrease in IgE synthesis, and alteration in T-lymphocyte activity. The principal and most effective route of allergen application is by subcutaneous injection. There are a great assortment of different allergen extracts available, but only standardized extracts should be used. In the United States, the Food and Drug Administration (FDA) determined that the intracutaneous technique should be used for assigning standardized unitage (i.e., bioequivalency allergy units [BAU]). Individuals with allergic rhinitis and/or asthma from tree and grass pollens in the spring, ragweed pollen in the fall and year-round dust-mite sensitivity who have had inadequate response to acceptable symptomatic medication and allergen avoidance are excellent candidates for immunotherapy. Immunotherapy is recommended for patients with allergic asthma unresponsive to allergen avoidance, even when symptomatic relief can be achieved with drug therapy. Treatment plans vary, but generally follow an initial dosing of short intervals (2 to 7 days) and should be increased 1.5 to 2 times with each injection if no reaction occurs. This dosing is followed by a maintenance dosage regimen at 3- or 4-week intervals and is determined by individual tolerance and relief of symptoms. Length of therapy varies from 3 to 5 years. The progress of the individual should be reviewed at regular intervals by the physician. Progressive improvement may be observed over the first 2 -to- 3 years of treatment. Discontinuation of therapy may be considered any time after a 2-to-3-year trial. The risk of relapse must be weighed against the individual's preference for continuation of therapy. Examples of potential allergens for which immunotherapy is effective include animal dander, animal feathers, animal fur, dust, grasses, insects, mites, molds, mushrooms, orris root, plants, pyrethrum, seeds, trees, vegetable gums, weeds, Hymenoptera or stinging insects (bees, hornets, wasps, fire ants).

Allergy Immunotherapy Administration Schedules

Injection Schedules	Description
There are two phase of allergy immunotherapy administration: • The initial build-up phase	Initial build-up phase: The dose and concentration of allergen immunotherapy extract are increased.

• The maintenance phase	Maintenance phase: the patient receives an effective therapeutic dose over a period of time. With the most common build-up phase schedule, injections are administered one to three times per week. With this schedule, patients usually reach a maintenance dose in three to six months, depending on the starting dilution and occurrence of reactions. If systemic reaction occurs, immunotherapy may be discontinued, or if continued, the dose is reduced. Immunotherapy schedules may need to be adjusted for a variety of reason, including missed visits, high pollen or mold seasons, addition of new allergen, or systemic reaction. One a patient reaches the maintenance phase, the interval between injections can be progressively increased as tolerated, to an interval of up to four weeks for inhalant allergens and up to eight weeks for venom. The effective therapeutic dose or maintenance dose is the dose that provides therapeutic efficacy without significant adverse local systemic reactions. Three to five years of maintenance therapy is generally considered optimal for maximum clinical benefit.
Accelerated immunotherapy schedules	Accelerated immunotherapy schedules include cluster immunotherapy and rush immunotherapy. Accelerated immunotherapy schedules may permit an individual to reach a maintenance dose sooner but are associated with a higher risk of systemic reactions for inhalant allergens, especially with high-risk patients (e.g., those with markedly positive prick/puncture or in vitro IgE test responses).
Cluster immunotherapy schedules	With cluster immunotherapy, several injections (usually two or three) are administered during each visit in order to achieve a maintenance dose more rapidly than conventional schedules. In cluster immunotherapy, several injections at increasing doses (generally 2–3 per visit) are administered sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is usually achieved more rapidly that with a conventional (single injection per session) schedule. Cluster schedules usually include fewer total injections than are used with conventional schedules and permit a patient to reach a maintenance dose sooner, usually in one to four weeks.
Rush immunotherapy schedules	With rush immunotherapy, incremental doses of allergen are administered at varying intervals between 15 and 60 minutes over one to three days

	until the target therapeutic dose is achieved. Rush immunotherapy for inhalant allergies may be associated with a significant risk of systemic reactions. Rush schedules for stinging Hymenoptera venom immunotherapy are not associated with an increased incidence of systemic reactions, however.

The major risk factor of allergy immunotherapy is anaphylaxis. Immunotherapy should be administered under the supervision of an appropriately trained physician who can recognize early signs and symptoms of anaphylaxis and administer emergency medications if needed.

Rapid Desensitization for Hypersensitivity Reactions

Rush allergen immunotherapy (rapid desensitization) for inhalant and venom allergens provide individuals with allergy symptom relief but in a shorter time frame than conventional therapy. Accelerated immunotherapy protocols allow individuals to reach therapeutic doses in a shorter time frame. The protocols of administration included 2 phases: an up-dosing phase that incrementally reaches the final dose resulting in a protective effect, and a maintenance phase in order to obtain the sustained effect. Although accelerated schedules offer the advantage of achieving the therapeutic dose much earlier than conventional immunotherapy schedules, they are also associated with an increased risk of systemic reactions.

For an allergy to a particular drug such as antibiotics, biologic and chemotherapeutic agents, drug desensitization may be utilized when there is no alternative medication or therapy available to treat a medical condition. Desensitization is an immunologic method that allows allergic individuals to receive the sensitizing drug safely. Drug desensitization involves the rapid administration of incremental doses of a specific drug for individuals with IgE antibodies to the drug that cannot be treated effectively with alternative medications.

Aspirin Desensitization

Aspirin is a widely used drug for aches, pains, and fever, one report estimates that 29 million people in the United States take aspirin tablets every day. Individuals with heart disease or who are at risk of getting heart disease or having a stroke take a daily aspirin. This helps keep their blood from forming clots that block blood vessels.

Some individuals react when they take aspirin or aspirin-type drugs (NSAIDs). A harmful reaction after taking aspirin or an aspirin-type drug involves respiratory (shortness of breath, wheezing and worsening of nasal/sinus symptoms) or skin symptoms (hives, itching or swelling). This is called and aspirin sensitivity.

Aspirin-exacerbated respiratory disease (AERD) is a condition that includes chronic asthma, and sinusitis with nasal polyps. Individuals with AERD experience respiratory symptoms from aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). Approximately one of 10 adults with asthma and one of three patients with asthma and sinusitis with nasal polyps are sensitive to aspirin and NSAIDs and have AERD.

People with AERD can undergo a procedure called aspirin desensitization which can induce tolerance to aspirin. To do this a physician in a controlled environment will complete a drug challenge with graded doses of aspirin over a period of several days. When the individual gets to the dose that causes the symptoms, the aspiring dosing will continue until the individual can tolerate the dose without adverse

reaction. The individual will continue to get higher and higher doses of the drug, as the individuals keeps getting the higher doses the body will start to accept the drug without reacting. Aspirin desensitization is generally done over a period of several days.

Alternative Allergy Immunotherapy Treatment Methods

Numerous alternative allergy treatment methods have been identified in the professional society guidelines and literature. These allergy treatment methods remain unproven at this time due to a lack of supporting evidence published in the peer-reviewed scientific literature. The role of these techniques in the management of allergic disease has not yet been established. Some of the alternative allergy treatment methods utilize extracts that are not U.S. Food and Drug Administration (FDA)-approved.

- Allergoids (modification of allergens to reduce allergenicity)
- Autogenous urine immunization (urine auto injection)
- Detoxification for allergies
- Epicutaneous immunotherapy
- Enzyme potentiated desensitization (EPD)
- Helminth Trichuris suis therapy for allergic rhinitis
- Homeopathic remedies for allergies
- Injection of food extracts
- Intranasal immunotherapy
- Low dose immunotherapy
- Multiple chemical sensitivity syndrome (environmental chemical avoidance for idiopathic environmental intolerances)
- Peptide therapy
- Provocation – neutralization therapy
- Rhinophototherapy
- Rotational and multiple food elimination diets (e.g., rotary diversified diet)
- Sublingual immunotherapy (SLIT) for food allergies

Regulatory Status

The Center for Biologics Evaluation and Research (CBER) regulates allergenic products.

Injectable allergen extracts are used for both diagnosis and treatment and are sterile liquids that are manufactured from natural substances (such as molds, pollens, insects, insect venoms, and animal hair) known to elicit allergic reactions in susceptible individuals. Injectable allergen extracts for food allergies are used only for diagnostic purposes. Among the injectable allergen extracts, some are standardized; for these products there is an established method to determine the potency (or strength) of the product on a lot-by-lot basis. For the other injectable allergen extracts there is no measure of potency, and these are called "non-standardized."

RATIONALE

This evidence review was created in April 1995 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 2026.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to

function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Allergy Immunotherapy (Subcutaneous)

Clinical Context and Therapy Purpose

The purpose of allergy immunotherapy (subcutaneous) is to provide a treatment option for individuals whose triggering allergens are not readily avoidable, the allergy is IgE-mediated as documented by skin testing or RAST, the symptoms are not easily controlled with medication and the patients are likely to cooperate in the treatment program.

The following PICO was used to select literature to inform this review.

Populations

Substances that cause this sensitivity or reaction are called allergens and may vary from naturally occurring materials, such as pollen and grass, to man-made materials, such as soaps or chemicals.

Individuals whose triggering allergens are not readily avoidable, the allergy is IgE-mediated as documented by skin testing or RAST, the symptoms are not easily controlled with medication, the symptoms encompass more than one season, and the patients are likely to cooperate in the program.

Interventions

The therapy being considered is allergy immunotherapy (subcutaneous).

Allergy immunotherapy (subcutaneous) 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.

Comparators

Standard care without allergen-specific immunotherapy.

First-line treatment includes avoidance and minimization of exposure when possible. Medication, including antihistamines, bronchodilators, leukotriene inhibitors, and steroids (cortisone), may be used to reverse some of the symptoms of allergic reactions.

Outcomes

The general outcomes of interest are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Most randomized controlled studies demonstrating efficacy with subcutaneous immunotherapy (SCIT), or sublingual immunotherapy (SLIT) have been conducted with single-allergen extracts. Although some guidelines have recommended against the use of multiple allergen mixes in treatment, allergists in the United States commonly administer a mixture of multiple allergens to which the patient is sensitive with the rationale that effective immunotherapy should include all major sensitivities. In 2009, Nelson et. al. reviewed the peer reviewed medical literature related to allergen immunotherapy studies. This review reported on the administration and clinical efficacy of the simultaneous administration of 2 or more unrelated allergen extracts using either subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). A total of 13 studies were identified, subcutaneous injections (n = 11), sublingual administration (n = 1), and both (n = 1). There were five studies identified with adequate information regarding the use of mixes of several (at least 2 or more) allergen extracts administered either by SCIT or SLIT immunotherapy. Three of these studies (D1, D2, D3) demonstrated that multiallergen immunotherapy was effective, and two of the studies did not. Outcomes related to the three effective studies found in D1 more children with asthma who received moderate-to-high doses of allergen (containing all of the inhalant allergens to which they were sensitive) were free of asthma after 4 years and on reaching age 16 years than were children with asthma who received placebo or very low doses of allergen; studies D2 and D3 with the complete removal of or 95% reduction in ragweed from multiallergen treatment resulted in the occurrence of significantly more symptoms the next pollen season. The latter finding clearly indicated that ragweed extract provided significant relief, despite its combination with multiple other extracts in the treatment program. In the two studies (D4 and D5) that did not show efficacy the limitations may have resulted in suboptimal outcomes may have been related to dose insufficiency or lack of treatment of key sensitivities. The authors concluded “the findings of the current review strongly suggest that the simultaneous delivery of multiple unrelated allergens can be clinically effective with the proper identification of relevant allergens, and treatment with adequate doses for a sufficient period of time is essential. However, there is a need for additional studies with more than 2 allergen extracts, particularly using sublingual administration, where there are currently no adequate studies to assess safety and efficacy.”

For individuals who have the following: food allergy, migraine headaches, vasomotor rhinitis, intrinsic (non-allergic) asthma, angioedema, atopic dermatitis and chronic urticaria currently there is paucity in the evidence in the peer reviewed medical literature as there were no studies identified that support SCIT is beneficial for these indications. In the guidelines from the National Institute of Allergy and Infectious Disease (NIAID) (Boyce et.al. 2010) states “immunotherapy for IgE mediated food allergies is not recommended, while this approach may show promise it is currently difficult to draw conclusions on the safety and whether clinical tolerance i.e., improvement in clinical symptoms that persists even after allergen specific immunotherapy is discontinued will develop with long-term treatment. Additional safety and efficacy data is needed before such treatment can be recommended.” Further studies are needed to determine safety and efficacy of using SCIT for these indications.

Section Summary: Allergy Immunotherapy (Subcutaneous)

Most randomized controlled studies demonstrating efficacy with subcutaneous immunotherapy (SCIT) have been conducted with single-allergen extracts. Although some guidelines have recommended against the use of multiple allergen mixes in treatment, allergists in the United States commonly administer a mixture of multiple allergens to which the patient is sensitive with the rationale that effective immunotherapy should include all major sensitivities. In Nelson et.al. 2009 there were five studies identified with adequate information and three of the five studies demonstrated that multiallergen immunotherapy was effective. This review strongly suggested that the simultaneous delivery of multiple unrelated allergens can be clinically effective with proper identification of relevant allergen and treatment with adequate doses is necessary for a sufficient period of time. However, there is a need for additional studies with more than 2 allergen extracts to assess safety and efficacy. In an updated consensus report by Burks et.al. 2013 from the American Academy of Allergy, Asthma and Immunology and European Academy of Allergy Clinical Immunology allergy immunotherapy (AIT) is an effective treatment for allergic asthma and rhinitis, as well as venom-induced anaphylaxis.

Currently there is paucity in the evidence in the peer reviewed medical literature addressing allergy immunotherapy (AIT) as a beneficial treatment for food allergy, migraine headaches, vasomotor rhinitis, intrinsic (non-allergic) asthma, angioedema, atopic dermatitis (except for dust mite atopic dermatitis), and chronic urticaria. Further studies are needed to determine safety and efficacy of AIT for these indications.

Rapid Desensitization

Clinical Context and Therapy Purpose

The purpose of rapid desensitization using rush/cluster allergen immunotherapy or drug desensitization is to accelerate the immune response to provide individual(s) with allergy symptom relief or alter drug hypersensitivity reaction to receive the drug safely.

The following PICO was used to select literature to inform this review.

Populations

Individuals with a IgE mediated hypersensitivity reaction:

- Allergy to a particular drug that cannot be treated effectively with alternative medications; *or*
- Insect sting (e.g., wasps, hornets, bees, fire ants) hypersensitivity (Hymenoptera); *or*

- Members with moderate to severe allergic rhinitis who need treatment during or immediately before the season of the affecting allergy.

Interventions

The therapy being considered is rush/cluster allergen immunotherapy (rapid desensitization) and drug desensitization.

Rush or cluster allergen immunotherapy (rapid desensitization) for inhalant and venom allergens provide individuals with allergy symptom relief but in a shorter time frame than conventional allergy immunotherapy. Accelerated immunotherapy protocols allow individuals to reach therapeutic doses in a shorter time frame. The protocols of administration included 2 phases: an up-dosing phase that incrementally reaches the final dose resulting in a protective effect, and a maintenance phase in order to obtain the sustained effect.

Although not considered an allergy immunotherapy the purpose of drug desensitization is a procedure that alters the immune response to the drug and results in temporary tolerance, allowing the individual with a drug hypersensitivity reaction to receive an uninterrupted course of the medication safely. Desensitization can be performed orally, intravenous (IV), intraperitoneal or subcutaneous (SQ).

Comparators

Individuals who have suffered a IgE mediated hypersensitivity reaction:

- Rush/cluster allergen immunotherapy (rapid desensitization): Conventional allergy immunotherapy (subcutaneous).
- Drug hypersensitivity: Rate of successful administration of the offending drug and the presence of breakthrough reactions (BTR) using a rapid desensitization protocol.

Outcomes

The general outcomes of interest are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Drug Hypersensitivity

Note: *See below for Aspirin Desensitization*

Khan et al (2022) performed an evidence review to inform drug allergy practice parameters. Most of the desensitization protocols published in the literature focus on antibiotics, but this principle has also been applied successfully to other drugs including biologic and chemotherapeutic agents. Desensitization is a procedure that alters the immune response to a hypersensitivity to a drug and results in temporary tolerance, allowing the individual to receive an uninterrupted course of the medication safely. Desensitization occurs usually when there is not an alternative medication that can effectively treat the individuals condition. Drug allergy reactions are generally immediate or delayed reactions. Immediate reactions are generally considered to occur within 1 hour but in some cases ≤ 6 hours of the exposure to the drug. Immediate drug reactions may include urticaria, angioedema, bronchospasm, or in severe cases, anaphylaxis. Delayed hypersensitivity reactions (HSRs) evolve over days or in some cases weeks following the exposure to the drug. Evidence for testing modalities for delayed HSRs is limited and of low certainty, generally based on small case series and without drug challenge. Drug skin testing and drug challenges are considered the reference standard for determining tolerance to a drug. Drug challenges can be performed for both immediate and delayed drug HSRs. One of the main approaches to treatment after a presumed drug HSR includes desensitization, which is reasonable and safe approach to care. There is limited data available on challenge or induction of tolerance procedures (desensitization) protocols, however, these limited studies were noted to have high success rates of 93% to 98%. See Practice Guidelines and Position Statements regarding the AAAI and ACAAI 2022 practice parameter regarding drug allergy for recommendations that include desensitization for specific antibiotics, biologic and chemotherapy agents.

Venom Hypersensitivity

Dhami et. al. in 2017 performed a systematic review and meta-analysis to assess allergy immunotherapy (AIT) effectiveness and safety in the management of insect venom allergy. Patients of any age with a physician-confirmed diagnosis of systemic sting reaction to a venom sting from bees, wasps or fire ants was included. Venom immunotherapy (VIT) considered was using different treatment protocols to include (conventional, cluster, rush and ultra-rush) administered through subcutaneous (SCIT) or sublingual routes (SLIT). The primary outcome was short - and long - term efficacy assessed by tolerated sting challenge or field sting; long-term was defined as sustained clinical efficacy after discontinuation of VIT. The secondary outcome measures were quality of life (QOL) and safety. The search identified 16,950 potentially eligible studies of which 17 articles satisfied the eligibility criteria and were included in this review. Of the 17 articles, 5 were systematic reviews in which 2 of these included meta-analyses, and the remaining 12 studies included five RCTs, three CBAs and four case series. Two case series and one controlled before and after (CBA) study addressed rush protocol. In the CBA study Pasaoglu et. al. 2006, the effectiveness of a seven-day rush protocol of VIT in 18 patients was evaluated. Seven patients received bee VIT, seven patients received yellow jacket VIT and four were controls. Of the 14 patients who received VIT, two experienced accidental stings (including a beekeeper who had multiple stings). No systemic sting reactions occurred. They concluded that a seven-day rush protocol is effective. This systematic review found that VIT was associated with a significant improvement in quality of life after 1 year for individuals receiving VIT as the VQLQ score of patients in the VIT arm improved. In the case series Stoevesandt et. al. (2014) evaluated the incidence of systemic reactions during 818 build-up cycles (rush five-day or ultra-rush three-day inpatient treatment protocol), and the severity of VIT-related anaphylaxis was graded according to the WAO classification system. The dates from this study indicated that rush protocols were safe with a very low number of patients suffering from moderate-to-severe systematic anaphylaxis (673 [82.3%]) of the 88 documented build-up cycles were tolerated without complications. The safety related to rush CIT protocol lasting an average of 7 days and monitored for local and systemic reactions during both the induction and maintenance phases over one year found that rush VIT was safe and associated with a low risk of systemic reactions (4 systemic reactions from a total of 469 injections, which factors out to be 0.85% risk per total number of injections. This treatment

approach can be considered for individuals requiring rapid protection such as those with a high risk of subsequent stings. Limitations of the systematic review include number of studies identified, and the low quality of the primary studies. The authors concluded for individuals that experience moderate-to-severe systemic reactions to venom they are likely to benefit from treatment with VIT (conventional or rush protocols). This benefit consists of reduction in frequency and severity of subsequent systemic reactions following future stings and/or improvement in QOL. “Given the paucity of high-quality evidence consideration needs to be given to undertaking high-quality RCT studies investigating the effectiveness of VIT. Related to VIT regimens at present many protocols for VIT are used discretionally at treatment centers with varying build-up and maintenance doses with no defined duration or treatment. These protocols very from conventional (12 weeks) to one day ultra rush protocols during the build-up phase.”

Moderate- to-Severe Allergic Rhinitis

Dykewicz et. al. in 2020 performed an evidence review to inform rhinitis practice parameter update. The recommendation regarding allergy immunotherapy (AIT) subcutaneous for the treatment of acute rhinitis (AR) states: “may be offered through shared decision making to patients with moderate/severe AR who are not controlled with allergen avoidance and/or pharmacotherapy; choose immunotherapy as the preferred method of treatment (e.g., due to the desire to avoid the adverse effects or long-term use of pharmacotherapy; and/or desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma.” In a 2013 Agency for Healthcare Research and Quality meta-analysis which reviewed 74 references and concluded “subcutaneous immunotherapy is effective in reducing symptoms of AR. The overall body of evidence showed that SCIT is safe and effective treatments for AR (moderate to high strength of evidence).” In a systematic review of the safety of SCIT “(45 of 74 SCIT studies reported safety data), the most common adverse events reported by 5% to 58% of patients were mild, local reactions. Pooled data found that general symptoms (headache, fatigue, arthritis) were reported by 44% of patients and respiratory related systemic reactions were reported following 15% of the injections. A survey by the American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology using the World Allergy Organization’s classification system for systemic reactions (grades 1-4) found an overall stable systemic reaction rate of 0.1%, 1 per 1 million allergy injections were associated with a grade 4 (most severe) reactions and 1 fatality per 23.3 million allergy injections. The decision to continue or discontinue treatment should be based on benefits sustained from treatment (improvement of QOL)” based on Visual Analogue Scale (VAS) and the Rhinoconjunctivitis Questionnaire.

Fan et. al. in 2015 noted there is a limited number of studies that have compared the efficacy and safety of conventional immunotherapy with cluster immunotherapy, in this study comparative analysis of cluster immunotherapy versus conventional immunotherapy in patients with allergic rhinitis (AR) was completed. A total of 60 patients with moderate to severe AR caused by dust mites were treated for one year with conventional immunotherapy (n =30) or cluster immunotherapy (n=30) and 9 of the 60 patients also suffered from asthma. This study was conducted as an open and comparative trial, with the treatment regimen chosen by each patient. In the conventional immunotherapy group all patients received the standard vaccine immunotherapy against dust mite allergen in which the maintenance dose was reached at 15 weeks. In the cluster immunotherapy group the initial dose included 2-3 injections performed 30 minutes apart weekly. The maintenance dose was reached after 6 weeks. To determine effectiveness of treatment nasal mucosa scores were recorded each visit according to the symptom and sign grading standards of allergic nasal mucosa inflammation for the following five symptoms: nasal itching, sneezing, nasal discharge flow, nasal obstruction and itching of the eye using the following grading system: 0, no symptoms; 1, mild symptoms (3-5 sneezes every day); 2, moderate symptoms (6-10 sneezes every day); and 3, severe symptoms (> 10 sneezes every day). Total score was calculated by totaling the symptom and sign scores. Effectiveness was evaluated according to the symptoms and signs prior to therapy, 6-weeks post treatment and 1 year post treatment. Safety evaluation was determined based on the patients

remaining in the clinic for at least 30 minutes following each injection and adverse events were recorded during this timeframe. Out of the 60 patients enrolled, 57 patients completed follow-up: cluster immunotherapy group (n=28) and conventional immunotherapy group (n=29). Following 6-weeks of treatment, the cluster immunotherapy group demonstrated a greater effect than the conventional immunotherapy group see Table 1 below. However, after 1 year of therapy the two treatment groups demonstrated equivalent levels of effectiveness see Table 2 below. Based on the one-year findings this likely due to the dose being much higher by the sixth week in the cluster immunotherapy group as compared to the conventional immunotherapy group which demonstrated that the cluster protocol improved symptoms faster and earlier in the treatment regimen.

Table 1. Comparison of Clinical Efficacy after 6-Weeks of Treatment

Group	Obviously Effective	Effective	No Effect	Total	Efficiency (%)
Cluster	14	10	4	28	85.71[a]
Conventional	8	7	14	29	51.72
Total	22	17	18	57	68.42

[a]P<0.01 versus the conventional group.

Table 2. Comparison of Clinical Efficacy after 1-Year of Treatment

Group	Obviously Effective	Effective	No Effect	Total	Efficiency
Cluster	**13**	**9**	**6**	**28**	**78.57[a]**
Conventional	12	10	7	29	75.86
Total	25	19	13	57	77.19

[a]P>0.05 versus the conventional group.

Adverse events during the dose accumulation phase and dose maintenance phase our outlined below in Tables 3, 4 and 5 below.

Table 3. Local Adverse Reactions Observed During Respective Dose Accumulation Stages of the Therapy Regimen

		Injection Number			Incidence of Adverse Reaction		
Group	**Cases**	**Accumulation**	**Maintenance**	**Total**	**Accumulation**	**Maintenance**	**Total**
Cluster	28	394	222	616	11 (2.79)	12 (5.41)	23 (3.73)
Conventional	29	445	193	638	15 (3.37)	11 (5.70)	26 (4.08)
Total	57	839	415	1,254			

Table 4. Systemic Adverse Reactions During Respective Dose Accumulation Stages of the Therapy Regimen

				Incidence of Adverse Reaction (%)		
Group	**Cases**	**Cases with Reactions (%)**	**Times of Injections**	**Grade I**	**Grade II**	**Total**
Cluster	28	3 (10.71)	394	3 (0.77)	2 (0.50)	5 (1.27)
Conventional	29	4 (13.79)	445	4 (0.90)	2 (0.45)	6 (1.35)

Table 5. Systemic Adverse Reactions During Respective Dose Maintenance Stages of the Therapy Regimen

				Incidence of Adverse Reaction (%)		
Group	**Cases**	**Cases with Reactions (%)**	**Times of Injections**	**Grade I**	**Grade II**	**Total**
Cluster	28	2 (7.14)	252	2 (0.79)	2 (0.79)	4 (1.58)
Conventional	29	4 (6.90)	193	4 (1.04)	1 (0.52)	3 (1.56)

Based on the summary of the study by the authors conventional immunotherapy requires more visits and the dose accumulation phase is long which may result in patients not wanting to be treated with conventional immunotherapy or are lost to follow-up. Cluster therapy can greatly reduce the duration of the dose accumulation phase getting the patients to the maintenance dose phase quicker. “Utilizing the cluster immunotherapy protocol the maintenance dose was reached at 6 weeks, reducing the dose accumulation phase by >60% compared to conventional immunotherapy protocol. All cases reached the dose maintenance phase and no severe complications or hospitalizations occurred. During the dose accumulation phase systemic adverse reactions occurred in occurred in 4 cases (13.79%) with six incidences (1.35%) in the conventional therapy group, and three cases (10.71%) with five incidences (1.27%) in the cluster immunotherapy group. The results of this study suggested that cluster immunotherapy is able to improve symptoms in patients with AR caused by dust mites, with no increase in adverse reactions. Therefore, cluster immunotherapy may be a rapid, effective, safe treatment for moderate- to -severe persistent AR.”

Section Summary: Rapid Desensitization

For individuals with a IgE mediated drug hypersensitivity reaction to drugs (i.e., antibiotics, biologics, or chemotherapy agents) in an evidence review performed by Khan et. al. 2022 to inform drug allergy practice parameters they found that evidence for rapid drug desensitization was generally limited and of low certainty, however, it is established treatment option in the United States designed to alter the immune response to the drug and results in temporary tolerance, allowing the patient with a drug hypersensitivity reaction to receive an uninterrupted course of the medication safely when cannot be treated effectively with alternative medications. See Practice Guideline and Position Statements.

For individuals with hypersensitivity to insect sting(s) (e.g., wasps, hornets, bees, fire ants) also known as hymenoptera, Dhami et. al. in 2017 performed a systematic review and meta-analysis to assess allergy immunotherapy (AIT) effectiveness and safety in the management of insect venom allergy (venom immunotherapy [VIT}). It was noted there was paucity of high-quality evidence regarding VIT, however, effectiveness of VIT for individuals that experience moderate-to-severe systemic reactions to venom are likely to benefit from treatment with VIT either conventional AIT or rush protocols. This is an established treatment option in the United States, in an updated consensus report by Burks et.al. 2013 from the American Academy of Allergy, Asthma and Immunology and European Academy of Allergy Clinical Immunology allergy immunotherapy (AIT) is an effective treatment for allergic asthma and rhinitis, as well as venom-induced anaphylaxis.

For individuals with moderate- to- severe allergic rhinitis (AR) including those individuals needing treatment during or immediately before the season of the affecting allergy, Dykewicz et. al. in 2020 performed an evidence review to inform the rhinitis practice parameter update in which allergy immunotherapy (AIT) may be offered through shared decision making to individuals with moderate-to-severe AR who are not controlled with allergen avoidance and/or pharmacotherapy. In 2015 Fan et. al. noted there is a limited number of studies that have compared the efficacy and safety of conventional immunotherapy with cluster immunotherapy in the treatment of moderate-to-severe AR, and completed a

comparative analysis study regarding cluster immunotherapy versus conventional immunotherapy in patients with AR. In this study they found “utilizing the cluster immunotherapy protocol the maintenance dose was reached at 6 weeks, reducing the dose accumulation phase by >60% compared to conventional immunotherapy protocol.” During the dose accumulation phase systemic adverse reactions occurred in 4 cases (13.79%) with six incidences (1.35%) in the conventional therapy group, and three cases (10.71%) with five incidences (1.27%) in the cluster immunotherapy group. The results of this study suggested that cluster immunotherapy is able to improve symptoms in patients with AR and "therefore, cluster immunotherapy may be a rapid, effective, safe treatment for moderate- to -severe persistent AR.”

Aspirin Desensitization

Clinical Context and Therapy Purpose

The purpose of aspirin desensitization is to induce tolerance to aspirin or aspirin-type drugs (NSAIDs) without adverse reaction.

The following PICO was used to select literature to inform this review.

Populations

Individuals with a harmful reaction after taking aspirin or an aspirin-type drug (NSAIDs) involves respiratory (shortness of breath, wheezing and worsening of nasal/sinus symptoms) or skin symptoms (hives, itching or swelling). This is called and aspirin sensitivity.

Interventions

Aspirin desensitization which can induce tolerance to aspirin or an aspirin-type drug (NSAIDs).

Comparators

Individuals who have suffered a harmful reaction after taking aspirin or an aspirin-type drug (NSAIDs) and rate of successful administration of the offending drug and the presence of breakthrough reactions (BTR) using a desensitization protocol. \

Outcomes

The general outcomes of interest are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. Follow-up over months to years is of interest to monitor outcomes.

Review of Evidence

Khan et al (2022) performed an evidence review to inform their drug allergy practice parameter update. Aspirin and NSAIDs can cause a range of drug hypersensitivities (HSRs) including exacerbation of underlying respiratory or cutaneous disease (urticaria, angioedema), anaphylaxis, and rarely, pneumonitis and meningitis. There are 4 primary categories of reactions that can be diagnosed via history, presence of comorbid diseases and drug challenges which include aspirin exacerbated respiratory disease (AERD), NSAID-induced urticaria and angioedema, NSAID-exacerbation cutaneous disease and single NSAID-induced reactions. A history of nasal polyposis with subsequent onset respiratory symptoms (chronic

rhinosinusitis and/or asthma) after aspirin or aspirin-type drug (NSAIDs) exposure suggests a diagnosis of AERD. AERD is unique and doesn't fit into the usual categories of adverse drug reactions the upper and lower respiratory tract symptoms are frequently sudden and often severe after the administration of aspirin or any aspirin-type drug (NSAIDs) that inhibits the COX-1 enzyme. In the treatment of AERD include the following recommendations:

- "Consensus-based Statement 23: We recommend against an oral aspirin challenge to confirm the diagnosis of AERD in cases of high diagnostic certainty based on clinical history; however, aspirin desensitization remains a therapeutic option when indicated". (Strength of Recommendation: Strong; Certainty of Evidence: Low)
- Consensus-based Statement 25: "We suggest that a challenge procedure be used to diagnose AERD when there is diagnostic uncertainty and that desensitization protocol be used with the intention is to place a patient on daily therapeutic aspirin dose for cardioprotection, pain relief, or to control nasal polyp regrowth." (Strength of Recommendation: Conditional; Level of Evidence: Moderate)

Desensitization protocols vary in dose, the protocol generally starts with milligram amounts to achieve the desired daily aspirin dose which is typically 325mg and can generally take 1-3 days to accomplish. If the final goal is 81 mg aspirin for antiplatelet effect, this can be the final dose of the desensitization, however, the patient will not be sensitized to a higher dose of aspirin or another NSAID. Higher doses may be required for management of nasal polyps and airway inflammation with an initial dose of 650 mg twice daily for optimal effect. A continued daily dose of the aspirin is required to remain in a tolerant state. Gaps in aspirin doses >48 hours may lead to loss of tolerance and after 5 days all patients will react to aspirin and require another desensitization procedure to resume therapy. Once patients are desensitized to aspirin there will be a universal tolerance to all COX-1 inhibiting NSAIDs achieved based on the dosage of aspirin desensitization. Precautions related to aspirin desensitization in AERD should include frequent monitoring of lung function and management of severe bronchospasms.

Section Summary: Aspirin Desensitization

While there may be paucity in the evidence regarding aspirin desensitization, based on the evidence review by Khan et. al. (2022) regarding aspirin and aspirin-type NSAIDs hypersensitivity and utilization of a desensitization protocol, based on the updated 2022 practice parameter by joint task force the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) for drug allergy, aspirin desensitization is an established treatment option in the United States for individuals with AERD with an aspirin hypersensitivity that require aspirin or aspirin or aspirin-type NSAIDs for cardio protection, pain relief, or to control nasal polyp regrowth. This was based on a conditional recommendation and moderate level of evidence. See Practice Guideline and Position Statements.

Alternative Allergy Immunotherapy Treatment Methods

Clinical Context and Therapy Purpose

Numerous alternative allergy treatment methods have been identified in the professional society guidelines and literature.

The following PICO was used to select literature to inform this review.

Populations

Individuals whose triggering allergens are not readily avoidable, the symptoms are not easily controlled with medication, and the symptoms encompass more than one season.

Interventions

Alternative allergy treatment methods:

- Allergoids (modification of allergens to reduce allergenicity)
- Autogenous urine immunization (urine auto injection)
- Detoxification for allergies
- Epicutaneous immunotherapy
- Enzyme potentiated desensitization (EPD)
- Helminth Trichuris suis therapy for allergic rhinitis
- Homeopathic remedies for allergies
- Injection of food extracts
- Intranasal immunotherapy
- Low dose immunotherapy
- Multiple chemical sensitivity syndrome (environmental chemical avoidance for idiopathic environmental intolerances)
- Peptide therapy
- Provocation – neutralization therapy
- Rhinophototherapy
- Rotational and multiple food elimination diets (e.g., rotary diversified diet)
- Sublingual immunotherapy (SLIT) for food allergies

Comparators

Standard care without allergen-specific immunotherapy.

First-line treatment includes avoidance and minimization of exposure when possible. Medication, including antihistamines, bronchodilators, leukotriene inhibitors, and steroids (cortisone), may be used to reverse some of the symptoms of allergic reactions.

Outcomes

The general outcomes of interest are symptoms, QOL, hospitalizations, medication use, and treatment-related morbidity. Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Allergoids

Allergoids are allergenic proteins that are treated with formaldehyde to produce larger molecules with decreased ability to react with IgE antibodies. Allergoids are licensed and manufactured for general distribution in Europe but are not available in the United States.

Autogenous Urine Immunization

Autogenous urine injection revolves around the theory that urine produced by the patient contains unspecified chemicals during an allergic reaction and that injection of these chemicals inhibits or neutralizes future allergic reactions. There is a lack of scientific evidence to support autogenous urine injections. Repeated injections of these antigens could induce autoimmune nephritis.

Detoxification

Detoxification is a method used by individuals who believe that an allergic state can be induced by toxic damage to the immune system from exposure to environmental chemicals. It is believed that certain lipid-soluble chemicals may be stored in body fat for long periods. Detoxification consists of sauna and exercise. The individual ingests high-dose niacin to induce erythema. Body fluids are replenished with water and electrolytes and certain essential oils are consumed, presumably to help replace fat-soluble chemical contaminants. This procedure takes approximately five hours and is repeated daily for 20–30 days. This form of therapy has not been well-studied and is unproven.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy involves the use of patches as a dosage form for allergen specific immunotherapy. An adverse effect of this therapy is patch-induced eczema at the patch site.

Systematic Review

Lee et. al. in (2022) completed a review related to recent advances in allergen-specific immunotherapy which included epicutaneous immunotherapy (EPIT). In this review related to the studies regarding EPIT it was found that studies did not compare the therapeutic efficacy of EPIT with that of conventional AITs such as subcutaneous allergy therapy, do did they measure CSMSs which are strongly recommended for evaluating the outcomes of AIT. The role of EPIT in alleviating food allergies found no study has compared the clinical outcomes of EPIT and conventional immunotherapy in patients with food allergies. The authors concluded the therapeutic efficacy of EPIT have not been established, although double-blinded placebo-controlled trials have shown it is a safe treatment. Further studies are needed to establish this novel AIT (EPIT) is safe and more effective than conventional ATIs.

Randomized Controlled Trials

Petroni et al (2024) conducted a randomized, double-blind, placebo-controlled dose-ranging clinical trial in children aged 2 to 17 years with an IgE mediated cow’s milk allergy (CMA) to assess the dose, efficacy

and safety of the epicutaneous immunotherapy utilizing Viaskin milk versus placebo. CMA was conducted between November 2014 through December 2017, and it took place at 17 trial sites in the US and Canada. The current CMA was confirmed by double-blind, placebo-controlled food challenge at study entry. Part A assessed the short-term safety of 150 µg, 300 µg, or 500 µg of Viaskin Milk; part B evaluated the efficacy and safety of the 3 doses versus placebo over 12 months of treatment. One hundred ninety-eight (n=198) met eligibility criteria (including an eliciting dose 300 mg or less) and were randomized. The primary outcome was the proportion of treatment responders, defined as a 10-fold or more increase in the cumulative reactive dose of cow's milk protein (reaching at least 144 mg) or a cumulative reactive dose of cow's milk protein at 1444 mg or more at the month 12 double-blind, placebo-controlled food challenge. A total of 95.5% of the randomized participants (mean [SD] age, 8 [4.17] years; 124 of 198 were male [62.6%]) completed treatment. The highest response rate was observed in participants who received Viaskin Milk at the 300-µg dose with 24 of 49 responders (49.0%) overall vs 16 of 53 responders (30.2%) in the placebo group (odds ratio, 2.19; 95% CI, 0.91-5.41; P = .09), highest in the 2 to 11 years age group (22 of 38 [57.9%] vs 13 of 40 [32.5%]; P = .04). Most treatment-emergent adverse events were mild or moderate application-site reactions. One participant in the 500-µg Viaskin Milk dose group experienced treatment-related anaphylaxis. Study authors concluded "in this randomized clinical trial, 12 months of daily epicutaneous immunotherapy with a dose of Viaskin Milk at 300 µg was associated with a statistically significant treatment response in 2- to 11-year-old children with IgE-mediated CMA. Treatment-related anaphylaxis and treatment-related discontinuation rates were low. Further research is needed to explore Viaskin Milk as a viable treatment option for children with IgE-mediated CMA." Limitations of this study included small sample size and participants with severe-life threatening anaphylaxis to cow's milk or uncontrolled persistent asthma were not eligible for participation which could have affected the results and could have limited generalizability.

Greenhawt et al (2023) conducted an industry sponsored phase 3, multicenter, double-blind, randomized, placebo-controlled trial (EPITOPE; NCT03211247) for children 1 to 3 years of age with confirmed peanut allergy verified through a double-blind, placebo-controlled food challenge to determine the efficacy and safety of epicutaneous immunotherapy (peanut patch nonoral immunotherapy). This trial included 51 sites in eight countries across the United States, Canada, Australia and Europe. The safe and appropriate dose of 250-ug was established in a previous sub study approved by an independent data and safety monitoring board. This trial was conducted under the investigational new drug application submitted to the U.S. Food and Drug Administration and with clinical trial approvals from review boards in Australia, Canada, and European site countries. The key inclusion criteria were a physician diagnosed peanut allergy i.e., a peanut specific IgE level greater than 0.7 kUA per liter and skin prick test with the largest wheal diameter of at least 6mm and eliciting dose of peanut protein of 300 mg or less. The patients underwent randomization in a 2:1 ratio to receive the peanut patch (n = 244) or placebo patch (n = 118) applied daily for 12 months. The first patch was applied for 3 hours under medical supervision and thereafter applied daily at home. The primary measure of treatment effect was the percentage of patients in the intervention group as compared with those in the placebo group who met the responder end point after 12 months of treatment. The response criterion was defined as the following: the baseline eliciting dose > 10 mg of peanut protein and the post-treatment eliciting dose was $\geq$ 1000 mg of peanut protein, or the baseline eliciting dose was $\leq$ 10 mg of peanut protein and the post-treatment eliciting dose was $\geq$ 300 mg of peanut protein. Secondary endpoints included change in cumulative reactive dose and eliciting dose from baseline to one-year. The primary endpoint was met as a greater percentage of patients using Viaskin Peanut met the responder end point 67% versus 33.5% (95% confidence interval [CI], 22.4 to 44.5; p < 0.001). The secondary endpoints at one year found patients using Viaskin Peanut had a median increase in eliciting dose of 900 mg (IQR, 90-1700 mg) from baseline compared with a median change of 0 mg (IQR, 0-700 mg) for patients using the placebo patch (p < 0.001). Median change in cumulative reactive dose from baseline to 1 year was 1300 mg (IQR, 140-3000 mg) for patients using Viaskin Peanut; patients using a placebo patch had a median change of 0 mg (IQR, 0-1000 mg) (p < 0.001). The most common adverse events in both groups were application site reactions such as erythema and

pruritis. Anaphylaxis occurred in 7.8% of patients using Viaskin Peanut and 3.4% of patients using the placebo patch. Eight patients using Viaskin Peanut discontinued due to an adverse event (application-site reactions, anaphylaxis, eczema). Limitations of this study included: patients with severe anaphylaxis were excluded which could limit generalizability; lack of racial diversity among patients; and the appropriate duration of peanut-patch use for maximal treatment response is unknown, and sustained effects after treatment cessation were not assessed. A 24-month open-label extension of EPITOPE trial to determine continued treatment response is ongoing (NCT03859700) and has enrolled 88% of all eligible EPITOPE trial participants.

Greenhawt et al (2025) assessed the interim efficacy and safety of Viaskin patch containing 250-ug of peanut protein (VP250) from the first year of Epitope open-label extension (OLE) study (year 2 results) (NCT03859700). The eligible participants enrolled in the OLE study for up to 3 years of total treatment with annual double-blind, placebo-controlled food challenges (DBPCFCs) and safety assessments. Standardized DBPCFCs were conducted in accordance with the Practical Allergy (PRACTALL) consensus report guidelines using a standardized food matrix. Increasing doses of peanut protein were administered every 30 minutes (1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg, and 2000 mg; cumulative dose of 3444 mg). Two hundred forty-four (n = 244) participants initiated the M24 DBPCFC (VP250 + VP250, n = 166; placebo + VP250, n = 78). The mean age of participant enrollment for both groups was 3.8 years. The assessment of evaluating treatment response at M24 included percentage participants who read eliciting dose (ED) $\geq$ 1000 mg and $\geq$ 2000 mg, and the percentage of participants that completed the DBPCFC without meeting the prespecified stopping criteria. The assessment for safety included adverse events (AE), assessment of local application site reactions, physical examination and clinical laboratory assessments. Of these 244 participants, 226 had evaluable data for all doses given, with 18 participants that partially completed the M24 DBPCFC (VP250 + VP250, n=14; placebo + VP250, n = 4). For the 24-month timepoint, 158 participants had evaluable data at both M12 and M24 for VP 250 (VP5250 + VP250 group) for the ED $\geq$1000 mg endpoint. The percentage of participants who achieved this endpoint increased significantly from 74.7% to 81%, Δ [M24-M12] = 6.3% (95% CI: 0%; 12.8%). An additional 25 participants achieved an ED $\geq$2000 mg at M24 who had not reached this endpoint at M12, representing a significant increase of 12.9% (95% CI: 5.6%; 20.0%), from 52.4% to 65.3% (among the 147 participants with evaluable data at both M12 and M24 for the ED $\geq$2000 mg endpoint). At the M24 DBPCFC, 85 of 152 (55.9%) participants ingested the full cumulative peanut protein dose (3444 mg) without meeting the prespecified stopping criteria. Among 147 participants with this endpoint evaluable at both M12 and M24 DBPCFC, a significantly greater proportion of participants achieved this endpoint at M24 than those at M12 (57.1% vs 39.5%, respectively; Δ [M24-M12] = 17.7% [95% CI: 9.3%; 25.6%]). The reactions elicited during the M24 DBPCFC decreased in severity compared with the M12 DBPCFC, at M24 severe reactions were reported in 6.0% (10 of 166) of VP250 participants compared with 13.3% (22 of 166) of VP250 participants at M12. The proportion of participants with absent or mild symptoms during the DBPCFC increased from 37.4% at M12 to 58.4% at M24. For the efficacy placebo + VP250 group there was an increase in the proportion of participants who achieved an ED $\geq$1000 mg from 30.1% (22 of 73) at M12 to 63.0% (46 of 73) at M24 (D[M24-M12] = 32.9% [95% CI: 20.5%; 43.5%]). Similarly, an additional 20 participants achieved an ED $\geq$2000 mg at M24 who had not reached this endpoint at M12, representing an increase from M12 to M24 of 27.8% (95% CI: 16.9%; 38.5%), from 9.7% to 37.5% among 72 participants. In the M24 DBPCFC, 38.5% of participants had absent or mild symptoms compared with 18.0% at M12. In the VP250 + VP250 group there were no treatment related anaphylaxis or serious treatment related adverse events. In the placebo treated group there was one treatment related anaphylaxis event. Study relevance limitations include that the enrolled population may not be representative of the general population due to their prior favorable treatment response and that the outcomes may have been affected due to COVID-19 pandemic interfering with scheduled study visits. The final results of EPITOPE OLE will be available at the completion of 3 years of treatment for all participants.

Pongracic et al (2021) conducted the REAL-Life Use and Safety of epicutaneous immunotherapy (EPIT) (REALISE) phase 3 multicenter, double-blind, placebo randomized controlled trial that assessed the safety of a patch containing 250-mg peanut protein (Viaskin Peanut 250 mg [VP250]) in children with peanut allergy. The trial was conducted under conditions that were close to anticipated real-world use, specifically relying on history and supportive testing. Additionally, the requirement for an entry or exit oral double-blind placebo-controlled food challenges (DBPCFCs) was removed because they are not used in routine clinical practice. The trial consisted of a six-month period followed by open-label active treatment and included patients (n=393) aged 4–11 years with a physician diagnosis of a peanut allergy. Patients were randomized to receive daily treatment with placebo (n=99) for six months or the VP250 patch (n=294) for up to 36 months. The primary safety outcome was measured at each visit and evaluated AEs and treatment emergent AEs (TEAEs) according to duration, severity, and causal relationship to treatment (related, probable, possible, unlikely, or not related), and those resulting in study discontinuation. Additionally, investigators assessed the severity of local skin reactions on a scale grade 0 (negative) to grade 4 (vesicles) and photographs of reactions were taken. Ten patients (2.5%) withdrew from the study: nine withdrew from the VP250 group and one from the placebo group. According to parent diary at the six-month follow-up, all participants receiving VP250 and 83.8% receiving placebo reported at least one occurrence of local skin reaction, with the frequency decreasing over time. Only four participants (1.4%) receiving VP250 discontinued because of adverse events (AEs). Seven children needed epinephrine for allergic reactions (not severe) attributed to VP250 with five continuing the study. Overall, AE rates were similar among participants with and without a history of peanut anaphylaxis. The authors concluded that the study demonstrated the safety, tolerability, and high adherence to treatment associated with the use of VP250. However, since the study was designed to replicate real-world conditions without a DBPCFC efficacy of treatment was not assessed. No health disparities were identified by the investigators; however, the majority of the patients were white males, and the results may not be applicable to other races or ethnic groups.

Fleischer et al (2020) published the two-year results of the PEOPLE study, which is a continuation of the PEPITES study, which was previously reported by Fleischer, et al., 2019. The open label PEOPLE study is designed to evaluate the long-term efficacy and safety of epicutaneous immunotherapy (EPIT) for the treatment of a peanut allergy. Patients who completed PEPITES were offered enrollment in PEOPLE. Patients entering PEOPLE received 24 months of open-label treatment if they were in the active treatment arm of PEPITES and will receive 36 months of open-label treatment if they were in the placebo arm of PEPITES. Subjects in both treatment arms will then have the option of a further 24 months of treatment, to a potential total active treatment time over PEPITES and PEOPLE of five years. The PEOPLE study population was comprised of two groups: the DBV712 250 mg group which included the patients who received active treatment in the PEPITES and the placebo + DBV712 250 mg group which included patients who received the placebo in PEPITES; this latter group are not reported in this publication. Of the eligible patients (n=213) who had received DBV712 250 mg in PEPITES, 198 (93%) entered PEOPLE. Patients were challenged to 5444 mg at month 36 of active treatment in PEOPLE. The patients that achieved an eliciting dose (ED) of > 1000 mg during the month-36 double-blind placebo-controlled food challenge (DBPCFC) were eligible to undergo an optional sustained unresponsiveness (SU) assessment, with an additional DBPCFC conducted after a two-month treatment discontinuation (during which time strict peanut avoidance was continued). One hundred and forty-one patients (71%) had assessable double-blind, placebo-controlled food challenge at month 36 with 51.8% (73 of 141) reaching the eliciting dose of > 1000 mg, compared with 40.4% (57 of 141) at month 12; and 13.5% (19 of 141) tolerated the full double-blind, placebo-controlled food challenge of 5444 mg. Local patch-site skin reactions were common but decreased over time. There was no treatment-related epinephrine use in years two or three. Compliance was high (96.9%), and withdrawals due to treatment-related adverse events were low (1%). While longer-term data with EPIT will continue to accumulate with the current study continuing to five years, the present results demonstrate that daily EPIT for peanut allergy beyond 1 year leads to continued response to treatment, with eliciting dose improvements that may translate into

increased protection from reactions due to accidental peanut ingestion. No health disparities were identified by the investigators; however, the majority of the patients were white males, and the results may not be applicable to other races or ethnic groups.

Fleischer et al (2019) assessed the efficacy and adverse events of epicutaneous immunotherapy using a peanut patch among peanut-allergic children. The phase 3, randomized, double-blind, placebo-controlled trial (PEPITES) included peanut-allergic children aged 4–11 years (n=356). Children did not have a history of a severe anaphylactic reaction, however developed objective symptoms during a double-blind, placebo-controlled food challenge at an eliciting dose of 300 mg or less of peanut protein. Patients were randomized to receive daily treatment with a peanut patch containing either 250 µg of peanut protein (n=238) or placebo (n=118) for 12 months. The primary outcome measured the percentage difference in responders between the peanut patch and the placebo patch based on eliciting dose (highest dose at which objective signs/symptoms of an immediate hypersensitivity reaction developed) which was determined by food challenges at baseline and at month 12. Participants with baseline eliciting dose of 10 mg or less were responders if the post treatment eliciting dose was 300 mg or more; participants with baseline eliciting dose greater than 10 to 300 mg were responders if the posttreatment eliciting dose was 1000 mg or more. A threshold of 15% or more on the lower bound of a 95% CI around responder rate difference was prespecified to determine a positive trial result. Adverse event evaluation included collection of treatment-emergent adverse events (TEAEs). Mean treatment adherence was 98.5% with 89.9% participants completing the trial. The responder rate was 35.3% with peanut-patch treatment vs 13.6% with placebo ($p<0.001$). The prespecified lower bound of the CI threshold was not met. TEAEs, primarily patch application site reactions, occurred in 95.4% and 89% of active and placebo groups, respectively. The all-causes rate of discontinuation was 10.5% in the peanut-patch group vs 9.3% in the placebo group. The authors concluded that the percentage difference in responders at 12 months with the peanut-patch therapy vs placebo was 21.7% which was statistically significant but did not meet the prespecified lower bound of the confidence interval criterion for a positive trial result. The clinical relevance of not meeting this lower bound of the confidence interval with respect to the treatment of peanut-allergic children with epicutaneous immunotherapy remains to be determined.

This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer reviewed scientific literature and is currently not approved by the U.S. Food and Drug Administration (FDA). Per a Hayes, Inc Emerging Technology Report results of the phase III EPITOPE trial was published in May 2023 (Greenhawt et. al. 2023, above), The U.S. FDA confirmed that the EPITOPE trial met prespecified criteria for efficacy, but additional safety studies are required to support a biologics license application (BLA) for the use of Viaskin Peanut patch in children aged 1 to 3 years with a confirmed peanut allergy.

Enzyme Potentiated Desensitization (EPD)

Enzyme potentiated desensitization is patented in Europe under the brand name of Epidyme. This immunotherapy consists of a mixture of allergens to molds, grass, weeds, trees, dust mites, dog and cat dander, and house dust. These allergens are administered in the doctor's office. While this is common practice in Europe, it is not on the United States market or regulated/approved by the U.S. FDA. The FDA has banned importation of EPD. There is a lack of clinical trials supporting the efficacy of this product.

Helminth Trichuris Suis Therapy for Allergic Rhinitis

Treatment with helminth trichuris suis has been proposed as a treatment for allergic rhinitis. A therapeutic approach has been suggested in different experimental models of allergic disease showing that live ova from trichuris suis, an intestinal helminth of pigs, can protect against allergic reactivity by helminth-

induced regulatory T cells and cytokines. Bager et al. conducted a double-blind, placebo-controlled study (n=100) to evaluate the effectiveness of trichuris suis therapy for the treatment of allergic rhinitis. The authors reported that repeated treatment with the helminth trichuris suis induced a substantial clinical and immunologic response but had no therapeutic effect on allergic rhinitis. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Homeopathic Remedies for Allergies

A homeopathic remedy administers a causative agent of a disease and is administered therapeutically in small amounts. There is no scientific evidence to support homeopathic practice as a method for treating allergies.

Injection of Food Extracts

An injection of food extracts consists of a combination of foods based on skin test results or a patient's report of intolerance to foods. There is a lack of clinical trials supporting this treatment.

Intranasal Immunotherapy

Treatment with intranasal immunotherapy has been proposed as a treatment for allergic rhinitis. Local adverse reactions are common with this approach and are the most frequent reason for discontinuing treatment. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Low Dose Immunotherapy or Ultra-Low Dose Enzyme Activated Immunotherapy/Low Dose Allergens (LDA)

Both methods involve the use of extremely low doses of antigens alone or in conjunction with beta-glucuronidase in an attempt to down regulate an inappropriate immune response. These allergy treatment methods remain unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Multiple Chemical Sensitivity Syndrome (environmental chemical avoidance for idiopathic environmental intolerances)

Multiple chemical sensitivity (MCS) (also known as idiopathic environmental intolerance (IEI), clinical ecological illness, clinical ecology, environmental illness, chemical AIDS, environmental/chemical hypersensitivity disease, total allergy syndrome, cerebral allergy, 20th century disease) has been used to describe a condition whereby an individual becomes chronically ill from exposure to chemicals in foods and the environment at doses far below the levels normally considered safe. Resulting “allergies” to these chemicals have been postulated to cause a number of troubling symptoms (e.g., fatigue, irritability, behavior problems, depression, confusion, and nervous tension in children) in the absence of objective physical findings. The existence of such a syndrome has been based on anecdotal reports and uncontrolled studies. Several well-designed investigations suggest that most people diagnosed with MCS have a medical or psychosomatic disorder that they cannot accept, preferring instead to interpret their symptoms as environmental sensitivities. If this is true, the diagnosis of MCS may delay proper medical and psychiatric care.

The theories and practices involving environmental allergies of this type have been severely criticized by the American Medical Association, the American College of Physicians, the Canadian Psychiatric

Association, the International Society of Regulatory Toxicology and Pharmacology, the American Academy of Allergy, Asthma and Immunology (AAAAI), and several scientific panels that have investigated them. Based on the reports in the peer-reviewed scientific literature, the American Medical Association's Council on Scientific Affairs stated that “there are no well controlled studies establishing a clear mechanism or cause for multiple chemical sensitivity syndrome.” The AAAAI reviewed the evidence again and concluded, “Rigorously controlled studies to verify the patient's reported subjective sensitivity to specific environmental chemicals have yet to be done. Moreover, there is no evidence that these patients have any immunologic or neurologic abnormalities. In addition, no form of therapy has yet been shown to alter the patient's illness in a favorable way.”

Confinement in an environmental control unit or facility (ecology unit), which has been used as a treatment for environmental illnesses and hypersensitivities, has not been established as an effective or appropriate treatment.

Peptide Therapy

The concept that the clinical response to allergen immunotherapy probably reflects the induction of non-responsiveness in Th2 lymphocytes led to the concept of immunotherapy with allergen-derived peptides representing T cell activating epitopes that do not react with IgE antibodies. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Provocation – Neutralization Therapy

This treatment involves the injection of substances under the skin that are suspected of triggering an allergic reaction in sufficient quantity to cause symptoms similar to the individual’s complaints. This is then followed by an immediate injection of a weaker or stronger dilution of the same antigen to relieve the symptoms. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Rhinophototherapy

Rhinophototherapy uses UV-B, UV-A, and visible light to treat allergic rhinitis. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Rotational and multiple food elimination diets (e.g., rotary diversified diet)

Proponents of the concept of multiple food allergies sometimes recommend a “rotary diversified diet,” in which the patient rotates foods so that the same food is eaten only once every 4–5 days to help identify foods that may cause allergic responses. This allergy treatment method remains unproven due to a lack of supporting evidence published in the peer-reviewed scientific literature.

Section Summary: Alternative Allergy Immunotherapy Treatment Methods

Numerous alternative allergy treatment methods have been identified in the professional society guidelines and textbook literature. These allergy treatment methods remain unproven at this time due to a lack of supporting evidence published in the peer-reviewed scientific literature. The role of these techniques in the management of allergic disease has not yet been established. Some of the alternative allergy treatment methods utilize extracts that are not U.S. Food and Drug Administration (FDA)-approved.

Sublingual Immunotherapy for Food Allergy

Clinical Context and Test/Therapy Purpose

The purpose of SLIT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with food allergy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with food allergy.

Interventions

The therapy being considered is SLIT.

Comparators

The following therapies and practices are currently being used to treat food allergies: SCIT and standard care without allergen-specific immunotherapy.

Outcomes

The general outcomes of interest are symptoms, quality of life, hospitalizations, medication use, treatment-related morbidity, and treatment-related mortality. Specific symptoms of interest are a reduction in the frequency of anaphylaxis, angioedema, bronchospasm/wheezing, and urticaria. Quality of life scales measuring the reduction in parental time off from work and expanded activities for a child would be of interest. The treatment-related morbidity outcomes are systemic reactions, skin reactions, gastrointestinal reactions, serious adverse events, and adverse events leading to treatment discontinuation. Desensitization is an intermediate outcome measure. Though not completely standardized, follow-up for allergic symptoms would typically occur periodically for months to years after starting treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

De Silva et al (2014) review identified 5 randomized trials of SLIT in patients with food allergies (fruit, peanut), 4 of which showed symptom improvement compared with placebo. The trial that did not demonstrate the benefit of SLIT compared with placebo was conducted in patients with apple allergy. All trials were considered low quality (eg, most did not include symptom assessments off treatment).

Additionally, Romantsik et al (2014) reported on a Cochrane review of oral immunotherapy and SLIT for egg allergy. No RCTs of SLIT were identified in their literature search (through November 2013).

Randomized Controlled Trials

Several RCTs have been published since the systematic reviews. Narisety et al (2015) published a double-blind RCT comparing oral immunotherapy with SLIT in 21 children who had peanut allergies.· Five (24%) children dropped out. Adverse events, generally mild, were significantly more common in the oral immunotherapy group. Among the remaining 16 patients, those in the oral immunotherapy group had a significantly greater challenge threshold at 12 months than those in the SLIT group (p=.01). However, only 4 patients (19%) had sustained unresponsiveness. Long-term, open-label follow-up of an RCT included in the da Silva systematic review assessing the effect of SLIT on peanut allergy reported a similar proportion of patients with sustained unresponsiveness (10/48; 21%).

An RCT by Burks et al (2015) reported on a placebo-controlled SLIT study in 40 patients (20 per group) with peanut allergy. At week 44, 14 (70%) in the SLIT group were considered responders compared with 3 (15%) in the placebo group. Seventeen patients in the placebo group crossed over to high-dose SLIT, and 7 (44%) were considered responders after 44 weeks.

No trials comparing SLIT with SCIT for the treatment of other food allergies were identified.

Interventional Study

Kim et al (2023) performed an open-label study of the safety, efficacy, and persistence of desensitization associated with SLIT in pediatric patients aged 1 to 11 years with peanut allergy. Patients received sublingual peanut protein in a build-up phase over approximately 5 months to a target maintenance dose of 4 mg once daily; treatment continued for a total of 48 months. Reaction thresholds to peanut were assessed by double-blind, placebo-controlled food challenges performed at baseline (as part of study screening), after 48 months of SLIT, and after a subsequent randomly-assigned avoidance phase of 1 to 17 weeks of peanut and SLIT avoidance. Clinically significant desensitization was defined as a successfully consumed peanut dose of at least 800 mg. Among 54 participants who received SLIT, mean age was 7.1 years; 47 participants completed SLIT and were included in the per-protocol analysis of desensitization at 48 months. Mean successfully consumed peanut dose increased significantly between baseline (48.4 ±93.2 mg) and 48 months (2723 ±1904 mg; p<.0001), with clinically significant desensitization achieved in 70.2% and no reaction throughout SLIT in 36% of participants. Among 37 patients who completed the post-SLIT avoidance phase, the median estimated time to loss of clinically significant desensitization was 22 weeks. Dosing symptoms (eg, oropharyngeal itching, lip swelling) were reported with 4.0% of home-administered doses; antihistamines were administered for symptoms associated with 0.14% of total doses administered, and no epinephrine was administered. Three patients withdrew from the study after initiating SLIT due to abdominal side effects.

Kim et al (2024) performed a double-blind study of the safety and efficacy of SLIT in pediatric patients aged 1 to 4 years with documented peanut allergy. The study was conducted at 2 US academic centers

and randomized 50 children to 4 mg peanut SLIT or placebo. Peanut protein was initiated at 2.5 mcg and escalated to 4 mg. At month 36, the double-blind food challenge was conducted to a cumulative dose of 4443 mg and administered in 7 doses as follows: 3, 10, 30, 100, 300, 1000, and 3000 mg. Those who tolerated at least 443 mg at month 36 then discontinued the study drug, avoided peanuts for 3 additional months, and returned for a final food challenge at month 39. The median cumulative dose tolerated in peanut SLIT participants was 4443 mg vs 143 mg for placebo at 36 months. At month 36, 60% of individuals in the peanut SLIT group ingested the full dose vs 0 placebo-treated patients when analyzed by ITT (p<.0001). At 39 months, 48% of peanut SLIT-treated patients were considered in remission compared with 0 placebo-treated patients, when analyzed by ITT. Oropharyngeal itching after dosing was significantly more common in peanut-treated patients (80% vs. 28%; p=.0005). No patients in either group required epinephrine, but 56% of patients in the peanut group and 36% of patients in the placebo group required an antihistamine within 2 hours of dosing.

Section Summary: Food Allergy

A few RCTs have evaluated SLIT for the treatment of food allergies. These trials had small sample sizes and tended to be rated as low quality by systematic reviewers. The available RCTs did not consistently find that SLIT was more effective than placebo or oral immunotherapy in patients with non-peanut allergies; in patients with peanut allergy, while available evidence consistently indicates efficacy of SLIT relative to placebo or pre-treatment baseline, SLIT has not been found to be as effective as oral immunotherapy. No RCTs were identified that compared SLIT and SCIT.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI)

In 2022, the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) updated their practice parameter regarding drug allergy which included the following consensus-based statements:

Section and Number	CBS	Strength of Recommendation	Certainty of Evidence
Drug Challenges			
CBS 1	We suggest that when the clinical probability of a drug allergy is low, in patients without	Conditional	Low

	contraindications for a drug challenge, that it be performed with a 1- or 2-step drug challenge		
CBS 2	We suggest that placebo-controlled drug challenges be considered in patients with a history of primarily subjective symptoms and/or multiple reported drug allergies	Conditional	Low
Testing for delay HSRs			
CBS 3	We suggest that for specific phenotypes of delayed drug HSRs where the pretest probability is high (eg, DRESS), but the implicated agent is uncertain, that dIDT and/or PT may be useful as adjunctive tests to support drug causality	Conditional	Low
Beta-Lactams i			
CBS 4	We recommend that a proactive effort should be made to delabel patients with reported penicillin allergy, if appropriate.	Strong	Moderate
CBS 5	We recommend against any testing in patients with a history inconsistent with penicillin allergy (such as headache, family history of penicillin allergy, or diarrhea), but a 1-step amoxicillin challenge may be offered to patients who are anxious or request additional reassurance to accept the removal of a penicillin allergy label.	Strong	Low
CBS 6	We suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated.	Conditional	Low
CBS 7	We recommend against the routine use of multiple-day challenges in the evaluation of penicillin allergy.	Strong	Low

CBS 8	We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as MDE and urticaria).	Strong	Moderate
CBS 9	We suggest that direct amoxicillin challenge be considered in adults with a history of distant (ie, >5 years ago) and benign cutaneous reactions (such as MDE and urticaria).	Conditional	Low
CBS 10	We suggest that for patients with a history of nonanaphylactic cephalosporin allergy, direct challenges (without prior skin test) to cephalosporins with dissimilar side chains be performed to determine tolerance.	Conditional	Moderate
CBS 11	We suggest that for patients with a history of anaphylaxis to a cephalosporin, a negative cephalosporin skin test should be confirmed prior to administration of a parenteral cephalosporin with a nonidentical R1 side chain.	Conditional	Low
CBS 12	We suggest that for patients with a history of anaphylaxis to a penicillin, a structurally dissimilar R1 side chain cephalosporin can be administered without testing or additional precautions	Conditional	Moderate
CBS 13	We suggest that for patients with a history of an unverified (not confirmed) nonanaphylactic penicillin allergy, a cephalosporin can be administered without testing or additional precautions.	Conditional	Moderate

CBS 14	We suggest that in patients with a history of an unverified nonanaphylactic cephalosporin allergy, a penicillin can be administered without testing or additional precautions	Conditional	Low
CBS 15	We suggest that in patients with a history of anaphylaxis to cephalosporins, penicillin skin testing and drug challenge should be performed prior to administration of a penicillin therapy	Conditional	Low
CBS 16	We suggest against penicillin skin testing in patients with a history of nonanaphylactic cephalosporin allergy prior to administration of a penicillin therapy	Conditional	Low
CBS 17	We suggest that in patients with a history of penicillin or cephalosporin allergy, a carbapenem may be administered without testing or additional precautions	Conditional	Moderate
CBS 18	We suggest that in patients with a history of penicillin or cephalosporin allergy, aztreonam may be administered without prior testing unless there is a history of ceftazidime allergy	Conditional	Moderate
CBS 19	We recommend that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy pathways to improve antibiotic stewardship outcomes	Strong	Moderate
Sulfonamides			

CBS 20	We suggest that for patients with a history of benign cutaneous reactions (eg, MDE, urticaria) to sulfonamide antibiotics that occurred >5 years ago, a 1-step drug challenge with TMPSMX be performed when there is a need to delabel a sulfonamide antibiotic allergy	Conditional	Low
Fluoroquinolones and macrolides			
CBS 21	We suggest using a 1- or 2-step drug challenge without preceding skin testing to confirm tolerance in patients with a history of nonanaphylactic reactions to fluoroquinolones or macrolides.	Conditional	Low
Aspirin/NSAID hypersensitivity phenotypes			
CBS 22	We suggest a selective COX-2 inhibitor may be used as an alternative analgesic in patients with any NSAID hypersensitivity phenotype when an NSAID is needed.	Conditional	Low
AERD			
CBS 23	We recommend against an oral aspirin challenge to confirm the diagnosis of AERD in cases of high diagnostic certainty based on clinical history; however, aspirin desensitization remains a therapeutic option when indicated.	Strong	Low
CBS 24	We suggest an oral aspirin challenge to confirm the diagnosis of AERD in cases of diagnostic uncertainty.	Conditional	Moderate
CBS 25	We suggest that a challenge procedure be	Conditional	Moderate

	used to diagnose AERD when there is diagnostic uncertainty and that a desensitization protocol be used when the intention is to place a patient on a daily therapeutic aspirin dose for cardioprotection, pain relief, or to control nasal polyp regrowth.		
Multiple NSAID-induced urticaria and angioedema			
CBS 26	For patients with NSAID-induced urticaria and angioedema, we suggest an oral aspirin challenge to identify whether the reaction is COX-1 cross-reactive.	Conditional	Low
Common NSAID hypersensitivity clinical scenarios			
CBS 27	We suggest a 2-step aspirin challenge for patients with a history of non-AERD aspirin allergy to aid in the management of cardiovascular disease events.	Conditional	Low
Cancer chemotherapeutic hypersensitivity			
CBS 28	We suggest that in patients with immediate reactions to chemotherapeutics a drug desensitization may be performed when the implicated drug is the preferred therapy.	Conditional	Low
CBS 29	We suggest that patients with nonimmediate reactions or a history of reactions inconsistent with chemotherapeutic hypersensitivity may be treated with a slowed infusion rate, graded dose escalation, and/or	Conditional	Low

	premedications without desensitization		
Platins			
CBS 30	We suggest that for patients with a history of immediate allergic reactions to platinum-based chemotherapeutic agents, the severity of the initial HSR and skin testing results (if available) may assist in their risk stratification and management.	Conditional	Low
CBS 31	We suggest that for patients with a history of immediate allergic reactions to taxane-based chemotherapeutic agents, the severity of the initial HSR may assist in their risk stratification and management.	Conditional	Low
Biologic hypersensitivity			
CBS 32	We suggest that patients with nonimmediate reactions or a history of reactions inconsistent with mAb hypersensitivity may be treated with a slowed infusion, graded dose escalation, and/or premedications without desensitization.	Conditional	Low
CBS 33	We suggest that for patients with immediate reactions or a history consistent with anaphylaxis to mAbs drug desensitization should be considered when the implicated drug is the preferred therapy.	Conditional	Low
Excipients allergy			
CBS 34	We suggest the clinician recognize that excipients are a very rare cause of immediate or delayed reactions associated with drugs. Still, excipient hypersensitivity may be	Conditional	Low

	considered in patients with a history of anaphylaxis to >_2 structurally unrelated drugs or products that share a common excipient (eg, injectable corticosteroids; PEG-based laxatives).		

I

n 2020, the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) updated their practice parameter regarding rhinitis that included the following recommendations:

- "We suggest that AIT (subcutaneous or sublingual tablets) be offered through shared decision making to patients with moderate/severe AR who (1) are not controlled with allergen avoidance and/or pharmacotherapy or (2) choose immunotherapy as the preferred method of treatment (e.g., due to the desire to avoid the adverse effects, costs, or long-term used of pharmacotherapy) and/or (3) desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma. (Strength of Recommendation: Conditional; Certainty of Evidence: Moderate)"
- "We suggest that AIT (subcutaneous or sublingual tablets) be considered for patients with controlled mild/moderate asthma with coexisting AR. (Strength of Recommendation: Conditional; Certainty of Evidence: Moderate)"

American Academy of Allergy, Asthma, and Immunology (AAAAI); American College of Allergy, Asthma, and Immunology (ACAAI); and Joint Council of Allergy, Asthma, and Immunology

In 2011, the allergen immunotherapy practice parameters were updated (third update) by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology with the following recommendations:

- Clinical trials do not support the use of subcutaneous immunotherapy for food hypersensitivity.
- Clinical studies do not support the use of allergen immunotherapy for chronic urticaria, angioedema or both and is not recommended.
- 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 3 to 5 years of treatment. Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. 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.
- The frequency of allergen immunotherapy administration during a conventional build-up phase is generally 1 to 3 injections per week.
- With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules.
- Rush schedules can achieve a maintenance dose more quickly than weekly schedules.
- Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased, as tolerated, up to an interval of 4 weeks for inhalant allergens and up to

8 weeks for venom. Some subjects might tolerate longer intervals between maintenance dose injections.

- The injection should be given subcutaneously.
- Immunotherapy is effective for pollen, animal allergens, dust mite, mold/fungi, 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.
- There are few studies that have investigated the efficacy of multiallergen subcutaneous immunotherapy. These studies have produced conflicting results, with some demonstrating significant clinical improvement compared with placebo and others showing no benefit over optimal pharmacotherapy and environmental control measures. Thus it is important to treat the patients only with relevant allergens.
- The selection of the components of an allergen immunotherapy extract should be based on a careful history in correlation with positive allergy skin test results or serum specific IgE antibodies. The allergen immunotherapy extract should contain only clinically relevant allergens. 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	0604U	Allergy and immunology (chronic recurrent angioedema), 4 bradykinin peptides, liquid chromatography and tandem mass spectrometry (LC-MS/ MS), whole blood, quantitative
	95115	Professional services for allergen immunotherapy not including provision of allergenic extracts; single injection
	95117	Professional services for allergen immunotherapy not including provision of allergenic extracts; 2 or more injections
	95120	Professional services for allergen immunotherapy in the office or institutions of the prescribing physician or other qualified health care professional, including provision of allergenic extract; single injection
	95125	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 2 or more injections
	95130	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; single stinging insect venom
	95131	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 2 stinging insect venoms
	95132	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 3 stinging insect venoms
	95133	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 4 stinging insect venoms
	95134	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; 5 stinging insect venoms
	95144	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single dose vial(s) (specify number of vials)

	95145	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy (specify number of doses); single stinging insect venom
	95146	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy (specify number of doses); 2 single stinging insect venoms
	95147	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy (specify number of doses); 3 single stinging insect venoms
	95148	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy (specify number of doses); 4 single stinging insect venoms
	95149	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy (specify number of doses); 5 single stinging insect venoms
	95165	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)
	95170	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; whole body extract biting insect or other arthropod
	95180	Rapid desensitization procedure, each hour (e.g., insulin, penicillin, equine serum)
	95199	Unlisted allergy/clinical immunologic service or procedure (e.g., sublingual immunotherapy)
HCPCS		
	A7023	Mechanical allergen particle barrier/inhalation filter, cream, nasal, topical
Type of Service	Medical	
Place of Service	Outpatient/Physician's Office	

POLICY HISTORY

Date	Action	Action
February 2026	Annual Review	Policy Revised

Date	Action	Action
February 2025	Annual Review	Policy Renewed
February 2024	Annual Review	Policy Revised
February 2023	Annual Review	Policy Revised
February 2022	Annual Review	Policy Revised
November 2021	Interim Review	Policy Revised
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Revised
February 2018	Annual Review	Policy Revised
February 2017	Annual Review	Policy Revised
April 2016	Annual Review	Policy Revised
January 2016	Interim Review	Policy Revised
May 2015	Annual Review	Policy Revised
May 2014	Annual Review	Policy Revised
July 2013	Annual Review	Policy Revised
September 2012	Annual Review	Policy Revised
September 2011	Annual Review	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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