Clinical Policy Title: **Allergen immunotherapy**

**Policy contains:** Desensitization; Hyposensitization; Immunoglobulin E.

AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

**Coverage policy**

Allergy immunotherapy is clinically proven and, therefore, medically necessary for allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity when all of the following criteria are met (Cox, 2011; Golden, 2016; Lin, 2018a):

- Demonstrated evidence of specific immunoglobulin E antibodies through immediate hypersensitivity skin tests or in vitro tests to specific immunoglobulin E.
- Symptoms are not reduced to an acceptable level by medication and the allergen cannot be avoided.
- Provider’s clinical judgment is that the amount and type of pharmacotherapy needed to control the symptoms are unacceptable.
- Provider’s clinical judgment is that the situation warrants the time and risk of providing immunotherapy.

The following therapies for allergen immunotherapy are investigational/not clinically proven and, therefore, not medically necessary:

- Allergoids or adjuvants.
- Autogenous urine immunotherapy.
- Bacterial immunotherapy.
- Enzyme potentiated desensitization.
- Food allergenic extract immunotherapy.
- Helminth Trichuris suis therapy for allergic rhinitis.
- Neutralization-provocation therapy.
- Non-subcutaneous routes of immunotherapy, including epicutaneous, intralymphatic, intranasal, oral, and sublingual swallow immunotherapy.
- Poison ivy, poison oak, and poison sumac extracts.
• Provocation/neutralization therapy, including intradermal, subcutaneous, and sublingual therapy.
• Repository emulsion therapy.
• Ultra-low-dose enzyme-activated immunotherapy or low-dose allergens.
• Whole-body extracts allergen immunotherapy for Hymenoptera sensitivity, except for fire ant extracts.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

Allergy immunotherapy is not considered necessary for all other conditions including:
• Angioedema.
• Chronic urticarial.
• Food hypersensitivity.
• Skin and mucous membrane disease, except as noted above for dust mite atopic dermatitis.
• Candida vulvovaginitis.
• Intrinsic asthma, not caused by allergy.
• Non-allergic vasomotor rhinitis.

Alternative covered services

Antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs, corticosteroids, adrenalin injector devices.

Background

Allergic response or hypersensitivity occurs when the immune system overreacts to an allergen by producing antibodies called immunoglobulin E, also known as IgE (Amarasekera, 2011). The antibodies move to cells that release chemicals, thereby causing an allergic reaction. Symptoms of a reaction may occur in the nose, eyes, lungs, throat, and skin. Immunoglobulin E is produced specifically in response to certain allergens, such that a person may react to one or more allergens but not others. The allergic response is understood to have evolved to be protective against helminth infections.

Allergen immunotherapy or hyposensitization, the repeated exposure of patients with immunoglobulin E-mediated conditions to specific allergens, may be effective in promoting protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens. This process may extend over a period of years, usually on an increasing dosage scale. This exposure is intended to build tolerance to the antigen, as evidenced by ability to tolerate higher doses with a concurrent decline in symptoms and need for medication. The need for immunotherapy is determined by diagnostic testing and clinical history of allergic responses. Effective immunotherapy is both preventive and curative (Pfaar, 2019). Allergen immunotherapy is generally a drawn-out process that is reserved for cases in which an allergen cannot be avoided.

Allergen immunotherapy is differentiated from the process of desensitization, which generally means a rapid progressive administration of an allergenic substance to reduce the response.
While many food allergens can be avoided with care, respiratory allergens are often more difficult to avoid. In many cases, food allergies resolve spontaneously. However, tree nut allergy, a potentially life-threatening condition that is prevalent in about 1 percent of the population, is outgrown in fewer than 10 percent of those affected (Smeekens, 2018).

**Findings**

Several guidelines, systematic reviews, and meta-analyses form the basis for this policy.

The Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology, issued an “Allergen Immunotherapy: A Practice Parameter Third Update” (Cox, 2011). This document recommends aeroallergen immunotherapy for patients with symptoms of allergic rhinitis or conjunctivitis, or asthma with naturally occurring exposure to allergens, when specific immunoglobulin E antibodies to the relevant allergen or allergens are demonstrated. Immunotherapy is also recommended for those with a history of a systemic reaction to Hymenoptera stings who demonstrate Hymenoptera-specific immunoglobulin E antibodies. Additionally, this guideline observed that there is some evidence of immunotherapy’s efficacy in patients with atopic dermatitis with aeroallergen sensitivity.

The Stinging Insect Hypersensitivity Practice Parameter Update 2016 workgroup issued refined guidelines (Golden, 2016) recommending venom immunotherapy for patients who have had a systemic insect sting reaction and who have a positive skin or in vitro test response. Extracts of honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venom are available for skin testing and venom immunotherapy. For those with suspected fire ant hypersensitivity, there is accumulating evidence for the efficacy of fire ant whole-body extract, which contains relevant venom allergens. Recommendations for immunotherapy with fire ant whole-body extract are generally the same as those for venom immunotherapy. The stinger (usually left in the tissue after an insect sting) should be examined to determine which insect is responsible for the reaction (Bilò, 2018).

**Allergic asthma and allergic rhinitis**

- An evaluation of the efficacy and safety of immunotherapy for allergic asthma published by the Agency for Healthcare Research and Quality (Lin, 2018a) found that, based on moderate-strength evidence, subcutaneous immunotherapy reduces the use of long-term control medications. Based on low-strength evidence, subcutaneous immunotherapy may improve quality of life, reduce the use of bronchodilators and for systemic corticosteroids, and improve forced expiratory volume. There was insufficient data to assess whether subcutaneous immunotherapy increases the risk of anaphylaxis. However, there was one case report of a death which was determined to possibly have been caused by subcutaneous immunotherapy.

- A European analysis (Asaria, 2018) found limited evidence for the cost-effectiveness of allergen immunotherapy, suggesting that it may be cost-effective for those with allergic rhinitis, with or without asthma, and in high-risk subgroups for venom allergy.

**Indications currently deemed investigational or ineffective**
Food allergies:
- The National Coverage Determination for Food Allergy Testing and Treatment (1988) deems sublingual intracutaneous and subcutaneous provocative and neutralization testing and neutralization therapy for food allergies not proven effective. Therefore they are excluded from Medicare coverage.
- A systematic review and meta-analysis (Chu, 2019) found that oral immunotherapy for peanut allergy unintentionally increased anaphylactic risk and frequency, epinephrine use, serious adverse events, and non-anaphylactic reactions, as compared to avoidance or placebo, even while it increased the likelihood of preventing out-of-clinic reactions (i.e., induced desensitization). Therefore, the treatment was not deemed safe.

Molds: Low-strength evidence (Di Bona, 2018) suggests that allergen immunotherapy with mold extracts is effective; however, studies of higher quality and larger samples are necessary to confirm this finding.

Sublingual administration: The use of sublingual administration of allergens is controversial.
- Two recent systematic reviews have found sublingual administration to be both effective and safe. Lin (2018b) examined sublingual immunotherapy for allergic asthma in studies of house dust mites, birch, and grass. Based on moderate-to-high-strength evidence, the results showed that sublingual immunotherapy improves the symptoms of allergic asthma, reduces long-term use of medication, and improves forced expiratory volume. Local and systemic reactions were common in both the treatment and control arms. Life-threatening reactions were few. Three cases of anaphylaxis and no deaths were reported in 20 randomized controlled trials and 10 observational studies (n = 3621). Blanco’s (2018) systematic review also found sublingual administration of immunotherapy both safe and effective for respiratory allergies.
- A statistically significantly higher (68 percent versus 29 percent, \( P < 0.01 \)) placebo effect has been observed in sublingual immunotherapy when compared to subcutaneous immunotherapy (Abramowicz, 2018).
- While the International Consensus Statement on Allergy and Rhinology (Wise, 2018) includes a strong recommendation for sublingual therapy in patients unable to get adequate relief from pharmacotherapy, they noted that the benefit of sublingual treatment over placebo is small, but tangible, with a lasting effect for 2 years after treatment, with minimal harm.
- Local Coverage Determination L37800 considers sublingual immunotherapy not reasonable and necessary as it has not been proven effective.

Billing and coding

Below are National Coverage Determinations, Local Coverage Determinations, and the most commonly submitted codes subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate Centers for Medicare & Medicaid Services references and coding manuals, and bill accordingly.

National coverage determinations

National Coverage Determination for Food Allergy Testing and Treatment (110.11)

Local coverage determinations

A52528 Allergen immunotherapy.
A56116 Allergen immunotherapy — new Part B LCD.
A54730 Allergen immunotherapy revision to the Part B LCD.
A56117 Allergen immunotherapy coding guidelines.
A56147 Allergen immunotherapy retired Part B LCD.
A56118 Response to comments: DL37800 Allergen immunotherapy.
L37800 Allergen immunotherapy.

ICD-10 diagnosis codes

H10.411 - H10.413  Opens in a new window Chronic giant papillary conjunctivitis, right eye - Chronic giant papillary conjunctivitis, bilateral
H10.419  Chronic giant papillary conjunctivitis,

CPT procedure codes

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
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 of biting insect or other arthropod (specify number of doses)
95180  Rapid desensitization procedure, each hour (eg, insulin, penicillin, equine serum)
95199  Unlisted allergy/clinical immunologic service or procedure

HCPCS level II codes

N/A

Policy updates
05/2019: Policy developed. Approved by the Clinical Policy Committee on

References

On May 9, 2019, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “allergy immunotherapy,” and “allergen immunotherapy.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.


Pfaar O, Bachert C, Bufe A, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int*. 2014;23(8):282–319. Doi: 10.1007/s40629-014-0032-2.


**Appendix**

No additional information was identified for this section during the writing of this policy.