Immunotherapy, Subcutaneous

ACG: A-0429 (AC)
Link to Codes

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Clinical Indications

- Subcutaneous immunotherapy may be indicated for **1 or more** of the following[A](2)(3)(4)(5):
  - Allergic rhinitis or conjunctivitis and **ALL** of the following(25)(26)(27)(28)(29)(30)(31):N
    - Age 2 years or older[B](4)(36)
    - Initial or subsequent course of treatment, as indicated by **1 or more** of the following:
      - Initial course of treatment, as indicated by **ALL** of the following:
        - Clinically complex allergic rhinitis, as indicated by **1 or more** of the following(21)(25)(28)(37)(38)(39):
          - Asthma exacerbations associated with allergic rhinitis(40)(41)
          - History of 2 or more seasons of allergy symptoms
          - Perennial allergy symptoms
        - Inadequate response to standard medical management interventions, including **ALL** of the following(21)(25)(28)(37)(38)(39):
          - Intranasal or oral antihistamine
          - Intranasal corticosteroid
        - Patient not pregnant at time of initiation of immunotherapy(31)(42)
        - Positive skin test or quantitative allergen-specific IgE antibody assay to agents suspected as allergic triggers(43)
        - Strong correlation between symptoms and suspected allergic triggers to **1 or more** of the following(2):
          - Animal allergens
          - Cockroaches
          - Dust mites
          - Grasses
          - Molds
          - Pollens
          - Trees
      - Subsequent course of treatment[C] is indicated if there has been favorable response to prior administration, as indicated by **1 or more** of the following(43)(44):
        - Decrease in amount of medication required to control symptoms
        - Improvement in clinical symptom scores
    - No concomitant administration of beta-blockers(36)

- No current clinically significant cardiovascular disease (eg, recent myocardial infarction, unstable angina, significant arrhythmia) or compromised pulmonary function (eg, asthma exacerbation or poorly controlled chronic obstructive pulmonary disease)(31)

− Asthma and **ALL** of the following(47)(48)(49):N
- Age 2 years or older[B](4)(36)
- Initial or subsequent course of treatment, as indicated by **1 or more** of the following:
  - Initial course of treatment, as indicated by **ALL** of the following:
    - FEV_1 70% or more of predicted(57)(58)
    - Inadequate response to standard medical management interventions, including **ALL** of the following(48)(56)(59)(60):
      - Avoidance of exposure to allergen triggers and irritants (eg, tobacco smoke)
      - Controller medication (eg, inhaled corticosteroids, leukotrienes, long-acting beta-agonist with corticosteroid, tiotropium)
      - Rescue medication(61)
    - Patient not pregnant at time of initiation of immunotherapy(42)
    - Positive skin test or quantitative allergen-specific IgE antibody assay to agents suspected as allergic trigger(43)
    - Strong correlation between symptoms and suspected allergic triggers to **1 or more** of the following:
      - Animal allergens
      - Cockroaches
      - Dust mites(55)(62)
      - Grasses
      - Molds
      - Pollens
      - Trees
  - Subsequent course of treatment[C] is indicated if there has been favorable response to prior administration, as indicated by **1 or more** of the following:
    - Decrease in amount of medication required to control symptoms and maintain peak flow rates or other measures of pulmonary function
    - Improvement in clinical symptom scores
- No concomitant administration of beta-blockers(6)(36)
- No current clinically significant cardiovascular disease (eg, recent myocardial infarction, unstable angina, significant arrhythmia) or compromised pulmonary function (eg, asthma exacerbation or poorly controlled chronic obstructive pulmonary disease)(3)

− Stinging insect hypersensitivity and **ALL** of the following(63)(64)(65):N
- Age 2 years or older[B](4)(36)
- Initial or subsequent course of treatment, as indicated by **1 or more** of the following:
  - Initial course of treatment, as indicated by **ALL** of the following:
    - Appropriate diagnostic test results, as indicated by **1 or more** of the following:
      - Positive skin test
      - Positive venom-specific IgE antibody assay[D]
    - Patient not pregnant at time of initiation of immunotherapy(42)
    - Systemic reaction to sting, as indicated by **1 or more** of the following:
      - Patient older than 16 years and systemic reaction limited to cutaneous signs and symptoms (eg, urticaria, pruritus, flush)[E]
      - Patient with systemic reaction to sting that included respiratory symptoms, cardiovascular symptoms, or both
  - Subsequent course of treatment is indicated if there has been favorable response to prior administration.
- No current clinically significant cardiovascular disease (eg, recent myocardial infarction, unstable angina, significant arrhythmia) or compromised pulmonary function (eg, asthma exacerbation or poorly controlled chronic obstructive pulmonary disease)

Alternatives

- Alternatives include:
  - For allergic asthma: inhaled beta-adrenergic agonists, inhaled or oral corticosteroids, leukotriene receptor antagonists, tiotropium, theophylline, mepolizumab, and omalizumab(56)(59)
  - For allergic rhinitis: antihistamines, nasal cromolyn, and intranasal corticosteroids(25)(26)(70)
  - Sublingual immunotherapy. See Immunotherapy, Sublingual AC for further information.

Evidence Summary

Background

Subcutaneous immunotherapy is a desensitization procedure that uses controlled exposure to known allergens to reduce the severity of subsequent allergic reactions associated with natural exposures to these allergens.(2)(6)(7) **(EG 2)** The most serious complication of subcutaneous immunotherapy is anaphylaxis; most serious systemic reactions occur within 30 minutes of injection.(6)(8)(9) **(EG 2)** Epicutaneous immunotherapy, which utilizes a patch to apply allergens to the skin, is currently being investigated as an alternative to subcutaneous immunotherapy.(10) **(EG 1)**

Criteria

The evidence for the clinical indications found in this guideline includes 49 published peer reviewed articles, 12 specialty society or other evidence-based guidelines, 3 Cochrane systematic reviews, and 2 book sections.

For allergic rhinitis or conjunctivitis, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review of 61 randomized controlled trials (6379 patients) evaluating the efficacy of allergen immunotherapy for allergic rhinitis found high-quality evidence that subcutaneous immunotherapy is associated with improvements in symptom scores and rhinitis/rhinoconjunctivitis medication usage.(29) **(EG 1)** A systematic review and meta-analysis including 46 randomized controlled trials compared (via adjusted indirect comparison) the effectiveness of either subcutaneous or sublingual immunotherapy for the treatment of adults with pharmacotherapy-refractory allergic rhinitis or rhinoconjunctivitis with or without asthma and found that both subcutaneous and sublingual immunotherapy were associated with improvements in symptom severity, allergy/asthma rescue medication usage, and quality of life (as measured by the Rhinoconjunctivitis Quality of Life Questionnaire); no significant differences were found between the 2 immunotherapy modalities. The authors noted that the analysis was limited by the heterogeneity in reported outcome measures in the included studies and the lack of randomized controlled trials that directly compared subcutaneous with sublingual immunotherapy; future studies were recommended.(32) **(EG 1)** An international consensus guideline recommends subcutaneous immunotherapy as a treatment option for adults and children with allergic rhinitis due to one or more identifiable allergen triggers.(28)(33) **(EG 2)** A specialty society guideline recommends allergen immunotherapy in pediatric patients with severe allergic rhinitis and grass or birch pollen allergy who are not adequately controlled with medical therapy as it may prevent the onset of asthma in the short term, in addition to improving allergic rhinitis symptoms and decreasing medication use. However, the guideline was unable to make a recommendation for or against the use of allergen immunotherapy for preventing asthma in the long term in patients with allergic rhinitis, for preventing asthma in adults with allergic rhinitis, or for patients with allergic rhinitis and allergy to allergens other than grass or birch pollen.(24) **(EG 2)** A specialty society guideline conditionally recommends subcutaneous allergen immunotherapy in patients with moderate to severe allergic rhinitis in whom the allergen trigger has been identified when symptoms are not controlled with allergen avoidance and pharmacotherapy or who prefer immunotherapy (eg, to avoid long-term use of pharmacotherapy), as well as in patients with coexisting controlled asthma and allergic rhinitis.(21) **(EG 2)**

For asthma, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A systematic review of allergen immunotherapy for asthma that included 54 double-blind randomized controlled trials (2305 patients) of subcutaneous immunotherapy for asthma reported that subcutaneous immunotherapy is associated with improvements in asthma symptom scores in the short term, asthma medication use, and disease-specific quality of life.(50) **(EG 1)** A systematic review of subcutaneous immunotherapy identified 38 randomized controlled trials addressing asthma (with and without concomitant rhinitis/rhinoconjunctivitis) and found high-grade evidence that immunotherapy reduces asthma symptoms and medication use.(47) **(EG 1)** A systematic review of immunotherapy for asthma evaluated data from 6 randomized controlled trials (404 patients) and reported that subcutaneous immunotherapy reduces the use of control medication over the long term; other randomized controlled trials provided lower-quality support for a beneficial impact on asthma-specific quality of life, rescue medication use, systemic corticosteroid use, and pulmonary function (ie, FEV_1).(51) **(EG 1)** A systematic review of 25 studies (17 randomized controlled trials) of subcutaneous immunotherapy for allergic asthma in pediatric patients reported moderate-strength evidence that subcutaneous immunotherapy improves long-term inhaled corticosteroid use.(52) **(EG 1)** An observational study that included 65,855 patients evaluated the safety of subcutaneous immunotherapy and found that patients with severe asthma (defined by ICD-9 billing codes) had similar rates of serious adverse events (defined as World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grade System grades 3 and 4) compared with patients without asthma.(53) **(EG 2)** However, review articles do not recommend administering subcutaneous immunotherapy to patients with severe or uncontrolled asthma due to the risk for anaphylaxis.(9)(54) **(EG 2)** A specialty society guideline recommends house dust mite subcutaneous immunotherapy for children and adults with controlled house dust mite-driven allergic asthma in addition to standard therapy, but notes that the available evidence is limited by heterogeneity in immunotherapy products and a lack of studies evaluating reduced asthma exacerbations or improved asthma control as primary outcomes.(55) **(EG 2)** An expert consensus guideline recommends the use of subcutaneous immunotherapy as an adjunct to standard therapy for individuals age 5 years or older with mild or moderate controlled allergic asthma.(48) **(EG 2)** An international consensus guideline recommends evaluating the potential risks and benefits of subcutaneous immunotherapy prior to deciding whether to initiate therapy for patients with allergic asthma.(56) **(EG 2)**

For stinging insect hypersensitivity, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Venom immunotherapy is strongly recommended for patients who have had systemic reactions to Hymenoptera stings, especially when associated with respiratory or cardiovascular symptoms, accompanied by positive skin tests or evidence of specific IgE antibodies.(64)(66) **(EG 2)** An evidence-based specialty society guideline notes that patients age 16 years or younger who present only with systemic cutaneous reactions without other manifestations to Hymenoptera or imported fire ants usually do not require venom immunotherapy. Some reports note that patients who have negative venom skin test results and negative venom-specific IgE test results have had subsequent systemic reactions to stinging insects. When patients experience a large local reaction, their risk of systemic reaction is 4%

to 10%. In adults with systemic cutaneous reactions without other manifestations, venom immunotherapy is considered optional rather than mandatory, and may be especially helpful in those patients who face unavoidable exposure, have comorbid conditions that increase their risk, or have impaired quality of life as a result of their venom sensitivity.(63) **(EG 2)** Another evidence-based specialty society guideline notes that venom immunotherapy for adults with generalized cutaneous reactions leads to significant improvements in quality of life as compared with adults who rely on epinephrine administration in response to insect sting.(64) **(EG 2)** Regarding a subsequent course of venom immunotherapy treatment, long-term follow-up studies suggest that a 5-year course appears to be better than 3 years, especially in patients at high risk (eg, frequent exposure, honeybee allergy, severe anaphylaxis).(63) **(EG 2)** However, treatment may be appropriately continued indefinitely in patients with a history of extreme or near-fatal anaphylaxis to a sting or in those with honeybee allergy.(63)(64)(67) **(EG 2)** A systematic review of randomized controlled trials concluded that venom immunotherapy is effective for the prevention of additional allergic reactions due to insect stings, with a small but significant risk of adverse systemic reaction.(68) **(EG 1)** A retrospective cohort study of 1532 patients who underwent sting challenge to evaluate the effectiveness of venom immunotherapy reported that predictors of treatment failure included allergy to honeybee venom, use of ACE inhibitor medication during sting challenge, high risk for systemic mastocytosis, and systemic allergic reactions during the buildup or maintenance phase of immunotherapy; chances of failure decreased with longer duration of immunotherapy.(69) **(EG 2)** However, the evidence evaluating the impact of ACE inhibitor medication is inconsistent, especially in patients who experience anaphylaxis and have comorbidities (eg, cardiovascular disease), as the benefits of venom immunotherapy may outweigh the risks.(63)(64) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For atopic dermatitis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis evaluating the efficacy of specific allergen immunotherapy for atopic eczema that identified 6 randomized controlled trials of subcutaneous immunotherapy concluded that immunotherapy could not be recommended for the treatment of atopic eczema due to the low quality of evidence; the authors recommended future large blinded randomized controlled trials to clarify the role of allergen immunotherapy for this disorder.(11) **(EG 1)** Although some studies indicate that immunotherapy can be effective for atopic dermatitis (eczema) when this condition is associated with aeroallergen sensitivity, the studies involve a small number of patients.(6)(12) **(EG 2)** A specialty society guideline recommends against the use of subcutaneous immunotherapy to treat atopic dermatitis.(13) **(EG 2)** Another specialty society guideline conditionally recommends adding immunotherapy to topical treatment for moderate to severe atopic dermatitis when patients are refractory to, intolerant of, or unable to use midpotency topical treatment; the guideline also recommends against adding immunotherapy for the treatment of mild atopic dermatitis.(14) **(EG 2)**

For chronic urticaria or angioedema, evidence demonstrates a lack of net benefit; additional research is recommended. **(RG C1)** Clinical studies do not support the use of allergen immunotherapy for chronic urticaria or angioedema.(4)(6) **(EG 2)**

For food allergy or hypersensitivity, evidence demonstrates a lack of net benefit; additional research is recommended. **(RG C1)** The primary treatments for food allergy include an avoidance diet as well as education about emergency measures to be taken in case of accidental food allergen ingestion.(15)(16) **(EG 2)** A review article notes that there are safety concerns regarding the use of subcutaneous immunotherapy for the treatment of food allergies due to the risk for anaphylaxis.(17) **(EG 2)** A phase III, double-blind, randomized controlled trial of 356 children age 4 to 11 years with peanut allergy comparing an epicutaneous patch with 250 mcg of peanut protein with placebo reported a statistically significant between-group difference in the proportion of patients who tolerated a double-blind placebo-controlled food challenge (35.3% vs 13.6%, respectively); however, the treatment effect was not considered clinically significant. The authors noted that the study excluded patients with a history of severe reactions (eg, anaphylaxis) to peanuts, which may have impacted the study results; further long-term studies are recommended.(18) **(EG 1)**

For latex allergy, evidence demonstrates a lack of net benefit; additional research is recommended. **(RG C1)** A review article identified only 3 randomized trials (64 patients) studying the use of subcutaneous immunotherapy for latex allergy, of which only one trial demonstrated improvement in symptoms; however, patients in all 3 trials experienced systemic reactions, with an incidence ranging from 47% to 82%. The authors noted that published guidelines do not support the use of subcutaneous immunotherapy for latex allergy.(19) **(EG 2)**

For local allergic rhinitis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** Local allergic rhinitis is defined as chronic rhinitis associated with a positive nasal allergen provocation test and local nasal mucosa production of allergen-specific IgE without markers of systemic atopy (ie, negative skin prick test and negative serum allergen-specific IgE).(20)(21) **(EG 2)** A systematic review and meta-analysis including 4 randomized controlled trials (134 patients) evaluated the effectiveness of either subcutaneous immunotherapy or placebo for the treatment of local allergic rhinitis and found that subcutaneous immunotherapy was associated with a reduction in rescue medication use and improvements in allergic symptoms, quality of life (as measured by the Rhinoconjunctivitis Quality of Life Questionnaire), and allergen tolerance compared with placebo. However, the authors noted that the analysis was limited by the small sample size and high variability in allergen dosing, treatment schedules, and scoring algorithms used in the included studies; larger, multicenter, longer-term, randomized controlled trials were recommended.(22) **(EG 1)**

For prevention of new allergen sensitization, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review assessing the efficacy of allergen immunotherapy in preventing the onset of new allergen sensitizations in patients with allergic rhinitis or asthma identified 12 studies (10,022 patients) that evaluated subcutaneous immunotherapy. Although there was low-quality evidence supporting allergen

immunotherapy, the authors cautioned that the findings were limited by bias and that further randomized controlled studies with longer follow-up are needed.(23) **(EG 1)** A specialty society guideline was unable to make a recommendation for or against the use of allergen immunotherapy for preventing later allergic manifestations in children with atopic dermatitis and other early atopic manifestations.(24) **(EG 2)**

Rationale

Use of this MCG care guideline helps the clinician determine if a particular treatment, medication, or service might be appropriate for a specific patient, taking into account their unique health complexities.

Use of these evidence-based clinical criteria to support decision making benefits the patient by identifying patient-specific complex clinical factors and conditions, promoting personalized treatment. Utilizing evidence-based clinical criteria promotes patient safety by helping ensure that potential patient benefits outweigh the risks. In addition, the use of evidence-based guidelines can increase consistency in treatment thresholds, leading to less variation in care and promoting equitable treatment among patients.

Related CMS Coverage Guidance

This guideline supplements but does not replace, modify, or supersede existing Medicare regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs).

Code of Federal Regulations (CFR): 42 CFR 419.22(71); 42 CFR 422.101(72)

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(73); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(74); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(75)

Medicare Coverage Determinations: Medicare Coverage Database(76)

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Footnotes

[A] Subcutaneous immunotherapy is associated with a small risk of serious systemic reaction, including anaphylaxis; most reactions occur within 30 minutes of injection. Patients should be observed in a healthcare setting for at least 30 minutes after an immunotherapy injection. Subcutaneous immunotherapy should be delivered in a setting with appropriate clinical staff and equipment to provide emergency treatment if needed.(1)(2) [A in Context Link 1]

[B] Specialty society guidelines state that allergen immunotherapy may be considered as a treatment option for selected children age 2 to 5 years.(6)(34) However, most studies evaluating allergen immunotherapy in children were conducted in patients age 5 years or older, and administration of subcutaneous immunotherapy may be distressing for very young children.(34)(35) [B in Context Link 1, 2, 3]

[C] Discontinuation of allergen immunotherapy should be considered after 3 to 5 years of ongoing treatment for inhaled allergens.(5)(6)(44)(45)(46) [C in Context Link 1, 2]

[D] Approximately 5% to 10% of patients with negative venom skin test results with a history of systemic reactions have a positive venom-specific serum IgE test result.(63) [D in Context Link 1]

[E] In adults with systemic cutaneous reactions without other manifestations, venom immunotherapy is considered optional rather than mandatory, and may be especially helpful in those patients who face unavoidable exposure, have comorbid conditions that increase their risk, or have impaired quality of life as a result of their venom sensitivity.(63) [E in Context Link 1]

Codes

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