Childhood Asthma: Treatment Update

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The prevalence of childhood asthma has risen significantly over the past four decades. A family history of atopic disease is associated with an increased likelihood of developing asthma, and environmental triggers such as tobacco smoke significantly increase the severity of daily asthma symptoms and the frequency of acute exacerbations. The goal of asthma therapy is to control symptoms, optimize lung function, and minimize days lost from school. Acute care of an asthma exacerbation involves the use of inhaled beta$_2$ agonists delivered by a metered-dose inhaler with a spacer, or a nebulizer, supplemented by anticholinergics in more severe exacerbations. The use of systemic and inhaled corticosteroids early in an asthma attack may decrease the rate of hospitalization. Chronic care focuses on controlling asthma by treating the underlying airway inflammation. Inhaled corticosteroids are the agent of choice in preventive care, but leukotriene inhibitors and nedocromil also can be used as prophylactic therapy. Long-acting beta$_2$ agonists may be added to one of the anti-inflammatory medications to improve control of asthma symptoms. Education programs for caregivers and self-management training for children with asthma improve outcomes. Although the control of allergens has not been demonstrated to work as monotherapy, immunotherapy as an adjunct to standard medical therapy can improve asthma control. Sublingual immunotherapy is a newer, more convenient option than injectable immunotherapy, but it requires further study. Omalizumab, a newer medication for prevention and control of moderate to severe asthma, is an expensive option. (Am Fam Physician 2005;71:1959-68, 1969. Copyright© 2005 American Academy of Family Physicians.)

▶ **Patient information:** A handout on treatment of childhood asthma, written by the authors of this article, is available on page 1969.

See page 1865 for strength-of-recommendation labels.

EB CME

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Asthma is a chronic lung disease characterized by recurrent cough and wheeze that is increasing in prevalence among children. More than 5 percent of the U.S. population younger than 18 years—nearly 5 million children—is affected by this disorder. It is found more often in patients with a personal or family history of atopy.[1] This article summarizes the treatment of asthma in children, with an emphasis on new modalities and the results of recent studies.

Development of Asthma

The development of asthma in children is thought to be the final step in a disease process described as the "allergic march." The allergic march may begin in infancy with food allergy–associated gastrointestinal disorders and dermatitis. Allergic rhinoconjunctivitis follows in early childhood, and asthma often completes the picture.[2] Early atopic dermatitis and elevated serum IgE antibodies against food allergens within the first two years of life, combined with family history, can be used to predict aeroallergen sensitization at five years of age.[3] Recent data from randomized controlled trials (RCTs) have suggested that early use of some antihistamines or immunotherapy may reduce the number of children who progress from rhinoconjunctivitis to asthma.[4,5]

Diagnosis

Asthma causes airway hyperresponsiveness, airflow limitation, and persistent respiratory symptoms such as wheezing, coughing, chest tightness, and shortness of breath. The majority of children with asthma develop symptoms before five years of age.[1] Because the symptoms vary extensively, asthma must be distinguished from other causes of respiratory illness. Demonstrating reversible airway obstruction in children old enough to perform peak flow measurements or spirometry provides an objective means of confirming the diagnosis. Once a child is diagnosed with asthma, the goal of therapy is to reduce wheeze and cough, reduce the risk and number of acute exacerbations, and minimize

Strength of Recommendations

Key clinical recommendation	*Label*	*References*
A spacer with a metered-dose inhaler is as effective as a nebulizer for delivery of a bronchodilator in the treatment of an acute asthma exacerbation and for the delivery of chronic prophylactic medications.	A	8
Physicians should consider adding inhaled ipratropium bromide (Atrovent) with each inhalation of a beta$_2$ agonist, particularly in the treatment of a more severe asthma exacerbation.	A	14
If possible, oral corticosteroids should be administered within 45 minutes of the onset of symptoms in an acute asthma exacerbation.	A	16
Modest doses of an inhaled corticosteroid are more effective than inhaled long-acting beta$_2$ agonists, inhaled nedocromil (Tilade), and leukotriene inhibitors in improving asthma symptoms and lung function in children with moderate persistent asthma and are recommended as the first-line treatment.	A	21, 22, 23
Parents and caregivers of children with asthma, particularly those with moderate to severe disease, should be taught to recognize and avoid triggers and to understand the use of prescribed medications and inhalation devices, and the importance of compliance and monitoring.	A	44

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. *See page 1865 for more information.*

adverse effects of treatments, sleep disturbances, and absences from school.[6] Treatment is tailored to the severity of asthma. The standard classification of asthma severity from the National Institutes of Health consensus guideline is shown in *Table 1*.[7]

Acute Therapy

BETA$_2$ AGONISTS

In an acute asthma exacerbation, inhaled beta$_2$ agonists are a mainstay of treatment *(Table 2)*.[7] Administration of an inhaled beta$_2$ agonist via a metered-dose inhaler with a spacer device is equally as effective as nebulized therapy.[8] There is no evidence to support the use of oral or intravenous beta$_2$ agonists in the treatment of acute asthma.[9] There is some evidence that high-dose nebulized beta$_2$ agonists (0.15 mg per kg per dose, approximately six puffs for a 35-kg [77-lb] child) administered every 20 minutes for six doses may be more effective than low-dose beta$_2$ agonists (0.05 mg per kg per dose, approximately two puffs for a 35-kg child) in treating severe acute asthma in children.[10] Levalbuterol (Xopenex), the nebulized levo-isomer of albuterol (Proventil), was compared with nebulized albuterol in one RCT; it showed a decrease in rate of hospitalization but no decrease in the length of hospital stay.[11]

SUPPLEMENTAL OXYGEN

Despite the absence of RCT data, it is common practice to use supplemental oxygen in children with acute asthma exacerbations treated in the emergency department. Low oxygen saturation measured with pulse oximetry has been correlated inversely with

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the rate of hospitalization.[12] However, poor sensitivity and specificity limit the use of oxygen saturation as a single indicator to determine the need for hospitalization.[13]

ANTICHOLINERGICS

The addition of inhaled ipratropium bromide (Atrovent) to each inhalation of a beta$_2$ agonist is more effective than the beta$_2$ agonist alone in children with an acute asthma exacerbation.[14] A systematic review of the evidence showed that one hospitalization is prevented for every 12 children treated with this therapy and one for every seven children with a severe exacerbation.[15]

CORTICOSTEROIDS

Oral corticosteroids given early during an acute asthma exacerbation (i.e., within 45 minutes of the onset of symptoms) reduce the likelihood of hospital admission.[16] In addition, oral corticosteroids are more effective than inhaled or nebulized corticosteroids in children hospitalized with severe acute asthma.[17] Repeated short courses of oral corticosteroids, at a dose of 1 mg per kg per day, in the treatment of acute flares of asthma do not appear to cause any lasting changes in bone metabolism, bone mineralization, or adrenal function.[18] There is no evidence that intravenous corticosteroids are any more effective than oral corticosteroids in children with an intact and functioning digestive tract.[7]

A systematic review of additional studies in the emergency department—including three pediatric studies—demonstrated that inhaled corticosteroids in high doses reduce hospital admission rates in patients with

TABLE 1
Long-Term Management of Asthma in Children

*Asthma classification**	*Symptom frequency*	*Lung function†*	*Medications required to maintain long-term control*
Mild intermittent	Daytime: 2 days per week or less Nighttime: 2 nights per month or less	PEF or FEV_1: 80 percent or more of predicted function	No daily medication needed
Mild persistent	Daytime: more than 2 days per week, but less than 1 time per day Nighttime: more than 2 nights per month	PEF or FEV_1: 80 percent or more of predicted function	Low-dosage inhaled corticosteroid delivered by nebulizer or metered-dose inhaler with holding chamber, with or without a face mask, or by dry-powder inhaler in children 5 years and younger
Moderate persistent	Daytime: daily Nighttime: more than 1 night per week	PEF or FEV_1: 60 to 80 percent of predicted function	Children 5 years and younger: low-dosage inhaled corticosteroid and long-acting beta$_2$ agonist *or* medium-dosage inhaled corticosteroid Children older than 5 years: low- to medium-dosage inhaled corticosteroid and long-acting inhaled beta$_2$ agonist.
Severe persistent	Daytime: continual Nighttime: frequent	PEF or FEV_1: 60 percent or less of predicted function	High-dosage inhaled corticosteroid and long-acting beta$_2$ agonist

PEF = peak expiratory flow; FEV_1 = forced expiratory volume in one second.

**—Clinical features before treatment or adequate control.*

†—Lung function measurements are used only in patients older than five years.

Adapted from National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics, 2002. Bethesda, Md.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 2003; NIH publication no. 02-5074:115.

acute asthma. However, there is insufficient evidence that inhaled corticosteroids alone are as effective as systemic steroids.[19]

THEOPHYLLINE

Although theophylline is not widely used in the treatment of childhood asthma, there is some improvement of symptoms and lung function with the use of intravenous theophylline in children hospitalized with a severe asthma attack. However, this therapy does not reduce the length of stay or the need for additional bronchodilator treatment, and it is not recommended for routine use.[20]

Long-Term Medical Therapy

CORTICOSTEROIDS

Inhaled corticosteroids are a standard part of maintenance therapy for asthma *(Tables 1, 3, and 4)*.[7] Studies have shown that, as a single agent, inhaled corticosteroids in a medium dosage are more effective than inhaled long-acting beta$_2$ agonists,

TABLE 2
Usual Dosages for Quick-Relief Asthma Medications

Medication	*Dosage form*	*Child dosage**
Inhaled medications		
Albuterol (Proventil)	HFA MDI with spacer: 90 mcg per puff, 200 puffs	1 to 2 puffs every 4 to 6 hours as needed.
	Nebulizer solution: 5 mg per mL (0.5 percent), 3.5 mg per 3 mL, 1.25 mg per 3 mL, 0.63 mg per 3 mL	0.05 mg per kg (minimum 1.25 mg, maximum 2.5 mg) in 3 mL of saline every 4 to 6 hours.
Ipratropium (Atrovent)	MDI with spacer: 18 mcg per puff, 200 puffs	1 to 2 puffs every 6 hours
	Nebulizer solution: 0.25 mg per mL (0.025 percent)	0.25 to 0.5 mg every 6 hours
Levalbuterol (R-albuterol, Xopenex)	Nebulizer solution: 0.31 mg per 3 mL, 0.63 mg per 3 mL, 1.25 mg per 3 mL	0.025 mg per kg (minimum 0.63 mg; maximum 1.25 mg) every 4 to 8 hours
Systemic corticosteroids		
Methylprednisolone (Medrol)	2-, 4-, 8-, 16-, and 32-mg tablets	0.25 to 2 mg per kg in the morning or every other day, as needed for control Short-course "burst": 1 to 2 mg per kg per day (maximum 60 mg per day) for 3 to 10 days
Prednisolone (Delta-Cortef)	5-mg tablets Syrup: 5 mg per 5 mL, 15 mg per 5 mL	Same as methylprednisolone
Prednisone	1-, 2.5-, 5-, 10-, 20-, and 50-mg tablets Syrup: 5 mg per mL, 5 mg per 5 mL	Same as methylprednisolone

HFA = hydrofluoroalkane; MDI = metered dose inhaler.

**—Dosages are for children 12 years or younger unless otherwise specified.*

Adapted from National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics, 2002. Bethesda, Md.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 2003. NIH publication no. 02-5074:120-1.

TABLE 3
Usual Dosages for Medications Used in the Long-Term Control of Asthma in Children

Medication	*Dosage form*	*Dosage**
Inhaled corticosteroids (see Table 4)		
Long-acting inhaled beta$_2$ agonists†		
Formoterol (Foradil Aerolizer)	DPI: 12 mcg per single-use capsule	1 capsule every 12 hours
Salmeterol (Serevent)	MDI: 21 mcg per puff	1 to 2 puffs every 12 hours
	DPI: 50 mcg per blister	1 blister every 12 hours
Combined medication		
Fluticasone/salmeterol (Advair Diskus)	DPI: 100, 250, or 500 mcg of fluticasone with 50 mcg of salmeterol	1 inhalation twice daily; dosage depends on severity of asthma
Cromolyn and nedocromil		
Cromolyn (Intal)	MDI: 1 mg per puff	1 to 2 puffs 3 to 4 times daily
	Nebulizer solution: 20 mg per ampule	1 ampule 3 to 4 times daily
Nedocromil (Tilade)	MDI: 1.75 mg per puff	1 to 2 puffs 2 to 4 times daily
Leukotriene modifiers		
Montelukast (Singulair)	4- or 5-mg chewable tablets, 4-mg packet of oral granules, 10-mg tablets	Age 12 to 23 months: 4 mg oral granules at bedtime
		Age 2 to 5 years: 4 mg at bedtime
		Age 6 to 14 years: 5 mg at bedtime
		Older than 14 years: 10 mg at bedtime
Zafirlukast (Accolate)	10- and 20-mg tablets	Age 7 to 11 years: 20 mg daily in divided doses (i.e., one 10-mg tablet twice daily)
		12 years and older: 20 mg twice daily
Methylxanthines‡		
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dosage is 10 mg per kg per day
		Usual maximums:
		Age < 1 year: (0.2 x [age in weeks]) + 5 = mg per kg per day
		Age ≥ 1 year: 16 mg per kg per day

DPI = dry-powder inhaler; MDI = metered-dose inhaler.

**—Dosages are for children 12 years or younger unless otherwise specified.*

†*—Should not be used for symptom relief or exacerbations. Use with an inhaled corticosteroid.*

‡*—Serum monitoring is important (serum concentration of 5 to 15 mcg per mL at steady state).*

Adapted from National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics, 2002. Bethesda, Md.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 2003; NIH publication no. 02-5074:133-5.

inhaled nedocromil (Tilade), and leukotriene inhibitors in improving asthma symptoms and lung function in children with mild to moderate asthma.[21-23] There also is less use of bronchodilators and oral corticosteroids in patients using maintenance inhaled corticosteroids.[24] Some short-term studies have found reduced growth velocity in children using inhaled corticosteroids regularly. However, multiple studies have found no evidence that children treated prophylactically with inhaled corticosteroids fail to reach their full adult height.[25,26]

TABLE 4
Estimated Comparative Daily Dosages of Inhaled Corticosteroids in Children 12 Years and Younger

Agent	*Low daily dose*	*Medium daily dose*	*High daily dose*
Beclomethasone CFC (Beclovent, Vanceril), 42 or 84 mcg per puff	84 to 336 mcg	336 to 672 mcg	> 672 mcg
Beclomethasone HFA, 40 or 80 mcg per puff	80 to 160 mcg	160 to 320 mcg	> 320 mcg
Budesonide (Pulmicort)			
DPI: 200 mcg per inhalation	100 to 200 mcg	200 to 400 mcg	> 400 mcg
Nebulizer solution: 0.25 or 0.5 mg per ampule	0.5 mg	1.0 mg	2.0 mg
Flunisolide (Aerobid), 250 mcg per puff	500 to 750 mcg	1,000 to 1,250 mcg	> 1,250 mcg
Fluticasone (Flovent)			
MDI: 44, 110, or 220 mcg per puff	88 to 176 mcg	176 to 440 mcg	> 440 mcg
DPI: 50, 100, or 250 mcg per inhalation	100 to 200 mcg	200 to 400 mcg	> 400 mcg
Triamcinolone acetonide (Azmacort), 100 mcg per puff	400 to 800 mcg	800 to 1,200 mcg	> 1,200 mcg

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane; DPI = dry-powder inhaler; MDI = metered-dose inhaler.

Adapted from National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma: update on selected topics, 2002. Bethesda, Md.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 2003. NIH publication no. 02-5074:135.

Unlike adults, children whose asthma is inadequately controlled with standard dosages of inhaled corticosteroids have not been shown to benefit from the addition of a long-acting $beta_2$ agonist or from an increase in the dosage of inhaled corticosteroids. In two RCTs,[21,27] benefit was demonstrated at three months with the addition of long-acting $beta_2$ agonists, but 12-month follow-up in one of these studies found no difference in objective measures of lung function, symptom scores, or exacerbation rate. One study[28] found that doubling the dosage of beclomethasone did not change objective measures of lung function or symptom scores but did result in a significant reduction of growth velocity. Some benefit can be achieved with the addition of oral theophylline, but long-term effects have not been assessed.[29] A brief, four-week study of oral montelukast (Singulair) added to standard dosages of inhaled budesonide (Rhinocort Aqua) in children whose asthma was not adequately controlled demonstrated improved lung function and a reduction in the number of days with asthma exacerbations.[30]

LEUKOTRIENE INHIBITORS

Retrospective observational studies have shown that optimizing the dosage of inhaled corticosteroids provides better control of asthma than oral montelukast.[23] However, one open-label, prospective, observational study[31] of children with mild asthma found that, in real-world conditions, montelukast and inhaled corticosteroids were equally effective, possibly because of significantly better adherence with oral montelukast therapy. Compared with placebo, oral montelukast reduces total daily use of $beta_2$ agonists, the need for rescue oral corticosteroids, and daytime symptom scores.[32,33]

NEDOCROMIL AND CROMOLYN

In children, inhaled nedocromil reduces asthma symptom scores, asthma severity, and bronchodilator use and improves lung function compared with placebo.[34] However, it is not as effective as inhaled corticosteroids. There is insufficient evidence to recommend prophylactic treatment with inhaled cromolyn (Intal) in children. Although it has been studied for use in children with asthma, it is less effective than inhaled corticosteroids in improving symptoms and lung function.[35]

LONG-ACTING BETA$_2$ AGONIST

Compared with placebo, salmeterol (Serevent) produces improved lung function in children, but there is conflicting evidence about whether it reduces the use of rescue or short-acting beta$_2$ agonists.[36] It was associated with a significant increase in bronchial hyperreactivity compared with inhaled corticosteroids.[36] It is not recommended for use as monotherapy in children with asthma. However, limited evidence from a single three-month study[27] with 210 patients shows that the combination of a long-acting beta$_2$ agonist and inhaled corticosteroids may increase the number of symptom-free days.

ORAL THEOPHYLLINE

Oral theophylline initially seemed promising in the prophylactic treatment of childhood asthma. When compared with placebo, it significantly increased the mean morning peak expiratory flow rate and reduced the mean number of acute nighttime attacks and doses of bronchodilator used.[37] However, it proved to be less promising when its use over one year was compared with the use of inhaled corticosteroids. Although there was no significant difference between theophylline and inhaled corticosteroids in reduction of asthma symptoms, there was an increased use of short-acting beta$_2$ agonists and oral corticosteroids in children receiving theophylline.[38] In summary, its use in children cannot be recommended because of the potential for serious side effects, such as cardiac arrhythmias or convulsions, if therapeutic blood levels are exceeded.[39]

IMMUNOTHERAPY

Immunotherapy can be used as an adjunct to standard drug therapy in allergic asthmatic children.[40] Sublingual (allergy drops) and injectable (allergy shots) therapies have been shown to reduce the presence of asthma and the overall use of asthma medication.[40,41] Standard immunotherapy has a 1.7 to 15 percent reported range of adverse effects, but between 1985 and 1989, there were 17 standard immunotherapy-related deaths reported in the United States.[42,43]

Other Interventions

EDUCATION

Educating parents and caregivers of children with asthma to recognize and avoid triggers, and to understand the use of prescribed medications, the proper use of inhalation devices, and the importance of compliance and monitoring, has been shown to improve lung function and decrease school absenteeism and visits to the emergency department.[44] Educational programs for the self-management of asthma by children and adolescents have similar outcomes.[45] Children with moderate to severe asthma receive the most benefit from educational programs.[44,45] The relative effectiveness of the various components of these programs has not been compared directly.[44] However, education for children who have received emergency department care for asthma does not reduce subsequent emergency department care, hospitalizations, or unscheduled doctor visits.[46]

Given the presence of safer and equally effective alternatives, oral theophylline cannot be recommended for long-term use because of the potential for serious adverse effects.

REDUCING ASTHMA TRIGGERS

Asthma triggers include allergens (i.e., dust, mites, pollen), irritants (i.e., smoke, perfumes), physical environment (i.e., exercise, cold air), physiologic triggers (i.e., viral infections), and pharmacologic therapies (i.e., beta blockers).[1] Environmental controls such as removal of carpeting in the child's bedroom, and the use of pillow and mattress covers and air filtration systems have been suggested as ways to reduce asthma symptoms.[47] However, recent evidence from better quality studies

has shown that dust-mite avoidance measures (using impermeable mattress and pillow covers) did not improve symptoms or reduce medication use in adults with moderate to severe asthma.[48] A similar study of children with allergic rhinitis showed no improvement in rhinitis symptoms using impermeable mattress and pillow covers compared with conventional covers.[49] The role of avoidance measures as an adjunct to pharmacotherapy or immunotherapy has not been well studied. There is insufficient evidence to recommend for or against the use of air filtration units to reduce allergen levels in an effort to improve asthma symptoms.[50]

SPACERS VS. NEBULIZERS

The use of a spacer with a metered-dose inhaler for delivery of the bronchodilator has been studied in inpatient, emergency department, and community settings in children as young as 10 months.[8,51,52] Metered-dose inhaler delivery of short-acting beta$_2$ agonists has been documented to be as effective as nebulizer delivery in the treatment of an acute asthma exacerbation and at a significantly lower cost.[51] In addition, children using a metered-dose inhaler plus a spacer have shorter stays in the emergency department and lower pulse rates than those using a nebulizer.[8] When a commercial spacer is unavailable, a device made from a 150-mL paper cup or a 500-mL plastic water bottle has been shown to be just as effective.[53] The dosage required for an acute exacerbation has not been well defined and, in studies of children, has ranged from three sprays administered separately to 10 puffs per dose sprayed all at once into the spacer.[54,55]

Spacers with metered-dose inhalers are as effective as nebulizers in the treatment of acute asthma exacerbations and result in shorter stays in the emergency department, lower costs, and a lower pulse rate.

Omalizumab and Sublingual Immunotherapy

Several new therapies have been introduced for the treatment of allergic asthma in children. Omalizumab (Xolair) is a recombinant DNA-derived humanized IgG monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It inhibits the binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils, limiting release of allergic mediators. Omalizumab is approved for use in children 12 years and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.[56,57] In children with moderate to severe asthma, omalizumab reduces the rate of serious asthma exacerbations and the need for physician or emergency department visits and hospitalizations, and improves asthma quality-of-life scores.[57] Although this new agent seems promising, its use is likely to be limited because it has an estimated cost of $10,000 per patient per year. Its use may be cost-effective if limited to allergic asthmatics who are poorly controlled on maximal therapy and who are hospitalized five or more times (or for 20 days or longer) per year.[58]

Sublingual immunotherapy (SLIT) improves asthma symptoms and reduces medication use compared with placebo in children with asthma who are allergic to house dust mites and in children with allergic rhinitis that is related to a variety of common inhalant allergens.[41,59] It appears to be safe, with unwanted effects being as low as 9.6 percent and no life-threatening adverse effects reported.[60] However, SLIT has not been compared directly with standard immunotherapy. While SLIT is a procedure and therefore is not regulated by the U.S. Food and Drug Administration (FDA), the extracts used for SLIT are FDA-approved for diagnosis and injectable immunotherapy only. Use of FDA-approved allergic extracts for SLIT is an off-label use. Health insurers consider SLIT investigational and do not cover its use.

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