Management of Allergic Asthma Including SCIT and SLIT

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Asthma in Special Populations
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1:30 p.m. – 2:30 p.m.
Management of Allergic Asthma Including SCIT and SLIT

Evaluate distinctive clinical and biomarker characteristics of allergic asthma.

Discuss optimal management and treatment strategies for achieving control of allergic asthma.

List relative and absolute contraindications for SCIT and SLIT.
Allergic Asthma

• A complex genetic disorder that involves interactions between genetic and environmental factors¹

• Most common phenotype in the general population of patients with asthma²

• Inflammatory disease regulated by the T helper (Th) cells³

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Allergic Asthma

• Allergen sensitization and Th2 responses are the major factors predisposing to the development of allergic asthma $^{1,2}$

• Th1/Th2 imbalance has been well documented in the pathogenesis of allergic asthma$^3$

• Allergic asthma is a complex inflammatory lung disease characterized by chronic airway inflammation and hyper-responsiveness


Clinical Characteristics of Allergic Asthma

• Clinical features of patients with asthma may differ depending on the sensitizing allergens

• Airways of patients with asthma may show infiltration of eosinophils, mucus overproduction, bronchial mucosal thickening, and bronchial wall remodeling

• T helper (Th) effector cells play a crucial role in the release of inflammatory cytokines and chemokines, mucus secretion, and airway hyperresponsiveness


Allergic Asthma Phenotypes

Two elements are recommended as necessary to identify the allergic asthma phenotype:

1. **allergic sensitization**
2. **symptoms in response to allergen exposure**

**Allergic sensitization:**
- Specific IgE -- demonstrated by skin prick-puncture tests or specific IgE in vitro tests-- to at least one of an appropriate panel of allergens

**Symptoms in response to allergen exposure:**
- Seasonal variation (not due to infection) and/or symptoms when exposed to freshly cut grass, house dust, molds, cats, dogs, or other furbearing animals. Allergic sensitization to these allergens also should be demonstrated.

Biomarkers of Allergic Asthma

Traceable substances used to examine organ function or other aspects of health\(^1\)

- Provide information to determine if a disease is present or absent.
- Define disease severity
- Provide information about its progression
- Serve to select the most effective treatment
- Serve as guidance for survival

Relevant biomarkers include:
- Eosinophil counts
- Fraction of exhaled nitric oxide (FENO) values
- Periostin
- IgE levels

### Biomarkers: Allergic Asthma and Eosinophilic Asthma

<table>
<thead>
<tr>
<th>Allergic Asthma</th>
<th>Eosinophilic Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>High eosinophilic inflammation</td>
<td>Eosinophilic inflammation</td>
</tr>
<tr>
<td>High serum IgE</td>
<td>High exhaled nitric oxide (FeNO)</td>
</tr>
<tr>
<td>High exhaled nitric oxide (FeNO)</td>
<td>Recurrent exacerbations</td>
</tr>
</tbody>
</table>
Management and Treatment Strategies for Achieving Asthma Control
Assessment of Asthma

1. Asthma control - two domains
   ◦ Assess symptom control over the last 4 weeks
   ◦ Assess risk factors for poor outcomes, including low lung function

2. Treatment issues
   ◦ Check inhaler technique and adherence
   ◦ Ask about side-effects
   ◦ Does the patient have a written asthma action plan?
   ◦ What are the patient’s attitudes and goals for their asthma?

3. Comorbidities
   ◦ Think of rhinosinusitis, GERD, obesity, obstructive sleep apnea, depression, anxiety
   ◦ These may contribute to symptoms and poor quality of life

Treatment of Allergic Asthma

Three treatment options for patients with allergic asthma:

- allergen avoidance
- pharmacotherapy including biologics
- allergen immunotherapy (AIT)

AIT consists of the repeated administration of one or multiple allergens to which the patient is sensitized.

Subcutaneous immunotherapy (SCIT) a solution containing an allergen(s) is injected under the skin.

Sublingual immunotherapy (SLIT), which may be dosed at home, consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue.

Optimal Management of Allergic Asthma

The management of allergic asthma includes the evaluation of various treatment options.

Three major management approaches:
- pharmacotherapy
- allergen immunotherapy
- allergen exposure reduction

Management plan must be individualized, implementing shared decision-making.
Disease severity, response or lack of response to previous treatment are important factor.

Stepwise management - pharmacotherapy

Step 1: Low dose ICS
- Consider low dose ICS
- Leukotriene receptor antagonists (LTRA)
- Low dose theophylline

Step 2: Low dose ICS/LABA**
- Med/high dose ICS
- Low dose ICS + LTRA (or + theoph*)

Step 3: Med/high ICS/LABA
- Add tiotropium*†
- Add low dose OCS
- Add SABA (or BDP/formoterol)

Step 4: Med/high ICS + LTRA (or + theoph*)
- Add low dose OCS
- Refer for add-on treatment e.g. tiotropium, anti-IgE, anti-IL5

Step 5: PREFERRED CONTROLLER CHOICE
- Add low dose OCS
- Refer for add-on treatment e.g. tiotropium, anti-IgE, anti-IL5

**Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations
Stepwise approach – pharmacotherapy (children ≤5 years)

**CONSIDER THIS STEP FOR CHILDREN WITH:**

- Infrequent viral wheezing and no or few interval symptoms
- Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year
- Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks.

**RELEVER**

- As-needed short-acting beta₂-agonist (all children)

**PREFERRED CONTROLLER CHOICE**

- Other controller options

**STEP 1**

- Daily low dose ICS

**STEP 2**

- Leukotriene receptor antagonist (LTRA)
- Intermittent ICS

**STEP 3**

- Double 'low dose' ICS
- Low dose ICS + LTRA

**STEP 4**

- Continue controller & refer for specialist assessment
- Add LTRA
- Inc. ICS frequency
- Add intermittent ICS

**STEP 1**

- Asthma diagnosis, and not well-controlled on low-dose ICS

**STEP 2**

- First check diagnosis, inhaler skills, adherence, exposures

**STEP 3**

- Not well-controlled on double ICS

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Allergic Asthma

- Severe allergic asthma: add-on anti-IgE (omalizumab ≥6 yrs)
- Severe eosinophilic asthma:
  - add-on anti-IL 5 (mepolizumab ≥12 yrs or reslizumab ≥18 yrs)
  - anti-IL5R (benralizumab ≥12 yrs)
- Sputum-guided treatment to reduce exacerbations and/or OCS dose
- Aspirin-exacerbated respiratory disease: consider add-on LTRA

Allergic Asthma: Non-pharmacological interventions

Comprehensive adherence-promoting program

Consider low dose maintenance oral corticosteroids

Asthma Education

Follow-up after an asthma exacerbation

Follow up all patients regularly after an exacerbation, until symptoms and lung function return to normal
- Patients are at increased risk during recovery from an exacerbation

The opportunity
- Exacerbations often represent failures in chronic asthma care, and they provide opportunities to review the patient’s asthma management

At follow-up visit(s), check:
- The patient’s understanding of the cause of the flare-up
- Modifiable risk factors, e.g. smoking
- Adherence with medications, and understanding of their purpose
- SABA is being taken only as-needed, not regularly
- Inhaler technique skills
- Written asthma action plan
Exhaled nitric oxide (FeNO)

Modestly associated with levels of blood and sputum eosinophils

FeNO is higher in:
- Asthma that is characterized by Type 2 airway inflammation
- Non-asthma conditions e.g. eosinophilic bronchitis, atopy, allergic rhinitis, eczema
- Late response to allergen (after 24 hours)

FeNO is lower in:
- Smokers
- Bronchoconstriction
- Early phases of allergic response
- Some asthma phenotypes, e.g. neutrophilic asthma

FeNO is increased or decreased in:
- Viral infections

Response to ICS
- In adult steroid-naïve patients with non-specific respiratory symptoms, FeNO >50ppb was associated with good short-term response to ICS
- No long-term studies examining the safety of withholding ICS if FENO is low
- FeNO cannot be recommended for deciding against treatment with ICS

## GINA assessment of symptom control

### A. Symptom control

In the past 4 weeks, has the patient had:

<table>
<thead>
<tr>
<th>Question</th>
<th>Well-controlled</th>
<th>Partly controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime asthma symptoms more than twice a week?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any night waking due to asthma?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliever needed for symptoms* more than twice a week?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any activity limitation due to asthma?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Excludes reliever taken before exercise, because many people take this routinely.

None of these 1-2 of these 3-4 of these
Assessing Symptom Control

A. Symptom control

<table>
<thead>
<tr>
<th>In the past 4 weeks, has the patient had:</th>
<th>Level of asthma symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well-controlled</td>
</tr>
<tr>
<td>• Daytime asthma symptoms more than twice a week?</td>
<td>Yes☒ No☐</td>
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B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV₁ at start of treatment, after 3 to 6 months of treatment to record the patient’s personal best, then periodically for ongoing risk assessment

**ASSESS PATIENT’S RISKS FOR:**
- Exacerbations
- Fixed airflow limitation
- Medication side-effects
Reasons for Poor Asthma Control

• Wrong diagnosis or confounding illness
• Incorrect choice of inhaler or poor technique
• Co-morbid conditions
• Unintentional or intentional nonadherence
• Individual variation in treatment response
• Under treatment
• Concurrent smoking

Critical Components of Management

• Provide guided self-management education

• Treat modifiable risk factors and comorbidities

• Advise about non-pharmacological therapies and strategies

• Consider stepping up if ... uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first

• Consider adding SLIT in adult HDM-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is 70% predicted

• Consider stepping down if symptoms are controlled for 3 months + low risk for exacerbations → stopping ICS is not advised

Treating Modifiable Risk Factors

Provide skills and support for guided asthma self-management
 ◦ This comprises self-monitoring of symptoms and/or PEF, a written asthma action plan and regular medical review

Prescribe medications or regimen that minimize exacerbations
 ◦ ICS-containing controller medications reduce risk of exacerbations
 ◦ For patients with ≥1 exacerbations in previous year, consider low-dose ICS/formoterol maintenance and reliever regimen*

Encourage avoidance of tobacco smoke (active or ETS)
 ◦ Provide smoking cessation advice and resources at every visit

For patients with severe asthma
 ◦ Refer to a specialist center, if available, for consideration of add-on medications and/or sputum-guided treatment

For patients with confirmed food allergy:
 ◦ Appropriate food avoidance
 ◦ Ensure availability of injectable epinephrine for anaphylaxis
Guided asthma self-management and skills training

Essential components are:

Skills training to use inhaler devices correctly

Encouraging adherence with medications, appointments

Asthma information

Guided self-management support

◦ Self-monitoring of symptoms and/or PEF
◦ Written asthma action plan
◦ Regular review by a health care provider
Strategies to improve adherence in asthma

- Shared decision-making
- Comprehensive asthma education with nurse home visits
- Inhaler reminders, either proactively or for missed doses
- Reviewing patients’ detailed dispensing records

Immunotherapy
Allergy Immunotherapy

1911

Noon and Freeman were the first researchers to test pollen allergen immunotherapy in a patient cohort.
Subcutaneous immunotherapy (SCIT)
Sublingual immunotherapy (SLIT)

**SCIT**
In 1911, Dr. L. Noon and Dr. J Freeman published their findings on allergy desensitization through subcutaneous injections of pollen extract.

By 1935, Cooke and colleagues identified a protective factor in serum, which was induced by AIT. This finding led to the concept of blocking antibodies.

**SLIT**
History of SLIT oral and sublingual route for the administration of allergen extracts was attempted in the 1900s, and the available vaccines were single allergen preparations (15); these efforts, however, failed to establish this method at the time.

In the 1980s, several landmark studies kept demonstrating the safety and effectiveness of SLIT.

Since 1986 there has been a revival of interest in SLIT.

Currently, there is no difference between the allergens used for SLIT and SCIT, although there are differences in the product quality requirements for each method.

Allergen Immunotherapy (AIT)

- Allergen immunotherapy (AIT) is the only class of treatment for allergy that has the potential to change the course of the disease.

- Immunological mechanisms of action involve induction of allergen-specific immune tolerance.

- AIT for allergic asthma is a potential therapeutic option in appropriately selected patients with allergic asthma.
Allergy Immunotherapy

Only class of treatment for respiratory allergy that has the potential to change the course of the disease\textsuperscript{1,2}

Effect of an established treatment of allergy immunotherapy for asthma was addressed through an international consensus guideline based on scientific evidence and expert opinion\textsuperscript{2}

European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the EAACI Guidelines on Allergen Immunotherapy for Allergic Asthma\textsuperscript{3}


Allergy Immunotherapy (AIT)

Modify the underlying cause of the disease, with proved long-term benefits

“Despite numerous clinical trials and meta-analyses proving AIT efficacious, it remains underused and is estimated to be used in less than 10% of patients with allergic rhinitis or asthma worldwide virtually no controversy about the use of AIT in the treatment of allergic rhinitis and allergic asthma” 1,2


Immunotherapy

• Immunotherapy is effective in the management of allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity.

• There is some evidence it might be effective in the treatment of atopic dermatitis in patients with aeroallergen sensitivity.

• Allergen immunotherapy might prevent the development of asthma in subjects with allergic rhinitis.

• Evaluation of a patient with suspected allergic rhinitis, allergic conjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests.

• A definitive diagnosis depends on the results of allergy testing (immediate hypersensitivity skin tests or in vitro tests for serum specific IgE)

https://doi.org/10.1007/s11882-018-0781-y
Indications for Immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or asthma

Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens.

Patient preference and acceptability
Adherence
Medication requirements
Response to avoidance measures
Adverse effects of medications
Coexisting allergic rhinitis and asthma
Possible prevention of asthma in patients with allergic rhinitis

(a) Immunological response by an allergic person

1. A person can become sensitized when exposed to, for example, grass pollen. White blood cells activate and accumulate in airway mucosa. Some of the white blood cells, B cells, start to produce IgE antibodies to grass pollen and release them into the blood.

2. Some IgE antibodies attach themselves to the surface of mast cells and basophils, which are filled with grains containing allergic mediators.

3. Repeated exposure to grass pollen leads to an immediate reaction, which is triggered by cross-linking of the cell-bound IgE and results in rapid release of allergic mediators.

4. Other white blood cells, T cells, drive a delayed and prolonged inflammatory reaction peaking some 6–10 h later with itching, swelling, and excessive secretions.

(b) Immunological response after allergy immunotherapy

1. As a consequence of treatment, T cells instruct some of the B cells to produce IgG antibodies instead of IgE antibodies.

2. IgG antibodies do not cause mast cell degranulation, but bind to allergen molecules, thereby blocking their binding to IgE, preventing cross-linking and release of allergic mediators.

3. Only a few allergen molecules are available for IgE binding and the allergic reaction is reduced or, in some cases, even discontinued.

4. As another consequence of the treatment, some T cells develop into regulatory T cells, which reduce antibody production in B cells, and effectively secure a diminished allergic immune response.

Larsen JN, Broge L, Jacobi H. Drug Discovery Today. 2016; 21, 26-37
Immunotherapy

• Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies

• Testing for serum specific IgE antibodies is useful under certain circumstances

• Immunotherapy should be considered when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure
Patient presents with allergic rhinitis, allergic conjunctivitis, allergic asthma or insect allergy

Not a candidate for immunotherapy

Administer Immunotherapy

Safety equipment and procedures in place
Medical personal appropriately trained to identify and treat immunotherapy reactions
At least 30 minute wait in office after injection

Reactions to immunotherapy injections?

YES

Manage reaction:
Reassess risk-benefit of immunotherapy
Consider dose/schedule adjustment
Consider discontinuing immunotherapy

NO

Follow-up every 6 to 12 months while on immunotherapy or more frequently for evaluation/management of immunotherapy reactions and/or underlying allergic disease or co-morbid conditions

Assess at follow up:
Clinical response to immunotherapy (e.g., symptoms, medication use)
Immunotherapy schedule, reactions, compliance
Continuation of immunotherapy treatment

Assess risks, benefits and costs of appropriate management options
Immunotherapy
Allergen exposure reduction
Medications
Patient preferences
Response to prior treatment
Severity of disease

Assess immunotherapy recommended for this patient?

NO

Immunotherapy not given

Obtain informed consent:
Counsel and educate patient about the benefits and risks of immunotherapy (including anticipated duration and onset of efficacy)

Identify:
Specific allergenic extracts
Starting dose and immunotherapy schedule
Maintenance dose

FIG 1. Algorithm for immunotherapy. (Continued.)
Subcutaneous Immunotherapy (SCIT)

Effective in patients with seasonal rhinitis (high-quality evidence)
Induces long-term remission (moderate evidence)
Effective in patients with perennial rhinitis (moderate evidence)
Indirect evidence suggests SCIT is more effective than SLIT in patients with SAR
Evidence base in children is less convincing; more studies are needed
Local side effects (pain and swelling) are common and well tolerated
SCIT requires administration in a specialist clinic
Adherence is easily monitored
Direct comparative evidence versus SLIT is weak, and definitive trials are needed
Some patients prefer SCIT (informed personal decision)

Sublingual Immunotherapy (SLIT)

Effective in patients with seasonal rhinitis (high-quality evidence)

Induces long-term remission (high-quality evidence)

Effective in patients with perennial rhinitis (high-quality evidence)

Indirect evidence suggests SLIT is better tolerated and safer than SCIT in patients with SAR

Evidence base in children is less convincing; more studies are needed

Local side effects (itching and swelling) are common and well tolerated

SLIT can be self-administered

Adherence can be a problem

Direct comparative evidence versus SCIT is weak, and definitive trials are needed.

Some patients prefer SLIT (informed personal decision)

Local Reactions

Delayed-onset systemic reactions might account for up to 50% of reactions. Delayed systemic reactions can occur without any preceding symptoms or can be part of a biphasic reaction. Several large studies demonstrate that life-threatening anaphylactic reactions after 30 minutes are rare. The recommendation that a patient should remain in the physician’s office/medical clinic for 30 minutes after the injection is unchanged from the previous update. It is recommended that at the onset of immunotherapy, patients should be counseled on the possibility of immediate and delayed systemic reactions during risk communication. An action plan for such an event should be discussed. The decision to prescribe epinephrine autoinjectors to patients receiving immunotherapy should be at the.....

Sublingual Immunotherapy (SLIT)

Consider adding SLIT in adult house dust mite-sensitive patients with allergic rhinitis who have exacerbations despite ICS treatment, provided FEV1 is 70% predicted

SLIT for house dust mite (HDM) is available in the US

Contraindications for SCIT and SLIT

- Uncontrolled asthma
- Difficult to control or severe asthma
- Pregnancy
- Acute infections
- Chronic urticaria, angioedema or both
- Malignant/cardiovascular/autoimmune disease
- SLIT should not be administered in case of acute inflammation, injury and surgical interventions in the oral cavity, or acute gastroenteritis
- Patients with negative test results for specific IgE antibodies or those with positive test results for specific IgE antibodies that do not correlate with suspected triggers, clinical symptoms, or exposure

Special considerations: Immunotherapy and Pregnancy

• Allergen immunotherapy can be continued but usually is not initiated in the pregnant patient” is unchanged from the previous update

• The update also suggests that discontinuation of immunotherapy should be considered if the pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic

Beta Blockers ACE-I and Immunotherapy

Most of the medical literature is limited to case reports and retrospective data. Initial reports suggested that beta-blockers were dangerous for patients at risk for anaphylaxis and ACE inhibitors were acceptable.

More recent data seem to indicate that beta-blockers may be safe for patients at risk for anaphylaxis and perhaps ACE inhibitors are worrisome. Some of this evidence is conflicting and there have not been definitive studies. Ultimately, prospective controlled trials are needed on this important topic.

There are data that beta-blockers may mask cardiac signs of anaphylaxis and blunt the response to epinephrine in cases of anaphylaxis.

It is recommended to avoid beta-blockers and possibly even ACE inhibitors for those patients at risk of anaphylaxis who lack cardiovascular disease.

However, for those patients with cardiovascular disease, beta-blockers and ACE inhibitors have been shown to decrease mortality and increase life expectancy.

Consideration should be given for patients with cardiovascular disease and venom immunotherapy to remain on their beta-blockers and ACE inhibitors.
Follow-up Care

Patients should be evaluated at least every 6 to 12 months while receiving immunotherapy to:

- Assess efficacy
- Implement and reinforce its safe administration
- Monitor adverse reactions
- Assess the patient’s adherence with treatment
- Determine whether immunotherapy can be discontinued
- Determine whether adjustments in the immunotherapy dosing schedule or allergen content are indicated
Summary

• Allergic asthma is a common asthma phenotype with distinctive clinical and biomarker characteristics.

• Defined based on the presence of allergic sensitization but may overlap with other phenotypes.

• Allergic asthma is heterogeneous regarding intensity of treatment required, clinical course, and outcomes.

• Allergen-specific IgE supported by detailed history is crucial to identify allergen sensitization and correlation of reported symptoms.

• Allergen immunotherapy is an effective immunemodulating treatment that should be recommended if pharmacologic therapy for allergic rhinitis is not effective or is not tolerated.

• Both SLIT and SCIT are effective for SAR.

• Both SLIT and SCIT induce long-term symptom remission.