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Review

Chinese Guideline on Allergen Immunotherapy for Allergic Rhinitis: The 2022 Update

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ABSTRACT

In the last few decades, there has been a progressive increase in the prevalence of allergic rhinitis (AR) in China, where it now affects approximately 250 million people. AR prevention and treatment include allergen avoidance, pharmacotherapy, allergen immunotherapy (AIT), and patient education, among which AIT is the only curative intervention. AIT targets the disease etiology and may potentially modify the immune system as well as induce allergen-specific immune tolerance in patients with AR. In 2017, a team of experts from the Chinese Society of Allergy (CSA) and the Chinese Allergic Rhinitis Collaborative Research Group (C2AR2G) produced the first English version of Chinese AIT guidelines for AR. Since then, there has been considerable progress in basic research of and clinical practice for AIT, especially regarding the role of follicular regulatory T (TFR) cells in the pathogenesis of AR and the use of allergen-specific immunoglobulin E (sIgE) in nasal secretions for the diagnosis of AR. Additionally, potential biomarkers, including TFR cells, sIgG4, and sIgE, have been used to monitor the incidence and progression of AR. Moreover, there has been a novel understanding of AIT during the coronavirus disease 2019 pandemic. Hence, there was an urgent need to update the AIT guideline for AR by a team of experts from CSA and C2AR2G. This document aims to serve as professional reference material on AIT for AR treatment in China, thus improving the development of AIT across the world.

Keywords: Allergen immunotherapy; allergic rhinitis; guidelines; China; immunoglobulin E; biomarkers; rush immunotherapy; house dust mites; subcutaneous immunotherapy

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INTRODUCTION

Allergen immunotherapy (AIT) is the most effective treatment for allergic rhinitis (AR) and can achieve long-term effects by modifying the natural progress of allergy. Standardized house dust mite (HDM) allergen extract was first available and authorized in China in 2004, and since then AIT has become an acceptable treatment option for AR. The first English language version of the Chinese AIT guidelines for AR treatment was produced in 2017 and covered the main aspects of AIT in China. However, basic research and clinical practice for AIT have progressed since then, necessitating updated guidelines. Therefore, a panel of experts from the Chinese Society of Allergy (CSA) and Chinese Allergic Rhinitis Collaborative Research Group (C2AR2G) have updated these guidelines. In addition to content from the first version, novel developments in AIT in China before and during the coronavirus disease 2019 (COVID-19) pandemic are discussed. This document aimed to serve as reference material for specialists, healthcare professionals, and organizations involved in AIT in China. Moreover, this document provides information to the international community on AIT strategies employed in China.

EPIDEMIOLOGY

AR prevalence

AR is a highly prevalent chronic disease, affecting 40% of the global population.[1] In China, it constitutes a huge economic burden of 51.28 billion EUR per year.[2] Additionally, an unexpectedly high prevalence of epidemiologic AR (18.6%–52.9%) and pollen-induced AR (PiAR, 10.5%–31.4%) were reported in 6 cities in the northern grasslands.[3] The prevalence of PiAR in urban areas (23.1%) was significantly higher than in rural areas (14.0%).[3] Unlike data for adults, most epidemiological studies on AR in children are limited to municipal or provincial administrative regions in the last 5 years (2016–2021). Recently published studies have indicated the prevalence of self-reported AR (28.6%) among children aged 6–12 years in Wuhan and physician-diagnosed AR in 0- to 17-year-olds (14.4%).[4,5] Interestingly, in most Chinese cities, 45% of AR outpatient visits occurred in August and September,[6] which could be attributed to the multi-sensitization and co-exposure to dust mites and some autumn allergens during this period. This inference was further supported by a recent study that listed HDM, *Artemisia, Humulus Japonicus, Alternaria alternata,* and *Cladosporium herbarium* allergens, as the 5 most common aeroallergens in China.[7]

Air pollution and AR

Similar to other allergic diseases, AR results from genetic and environmental factors. In recent years, due to rapid socio-economic development and continuous ecological degradation, air pollution is becoming a serious threat to human health. Air pollutants related to allergic diseases include particulate matter (PM), nitrogen oxides (NO_x), sulfur dioxide (SO_2), carbonic oxide (CO), ozone (O_3), and environmental tobacco smoke. Among them, PM ≤ 2.5 μm (PM2.5) in aerodynamic diameter can deposit in the alveoli, enter the circulatory system through the respiratory barrier, and spread to the whole body, triggering numerous allergic diseases. *In vitro* and animal studies have shown that air pollutants and allergens may have synergistic adverse effects during the development of allergic respiratory diseases.[8,9]

An increasing number of epidemiological studies have shown that air pollution is a risk factor for AR. Aerial PM concentration is related to the incidence of AR outpatients.[10-12] Chu *et al.*[12] reported

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that the interquartile range in PM10 (difference of estimates, 5.86%; 95% confidence interval [CI], 3.00–8.81; $P = 4.72 \times 10^{-5}$) and PM2.5 (difference of estimates, 5.39%; 95% CI, 2.73–8.12; $P = 5.67 \times 10^{-5}$) concentrations were positively associated with the number of AR patients, with 3-day cumulative effects in a single-pollutant model. Additionally, PM2.5 induces substantial goblet cell hyperplasia, collagen deposition, eosinophil production, and immunoglobulin E (IgE) protein expression; moreover, PM2.5 exacerbates the symptoms of AR in animal models.[13-15] The role of other air pollutants on the incidence and severity of AR has also been examined. Sun *et al.*[16] reported that O_3 increases sneezing frequency and the expression of type 2 T-helper (Th2) cytokines, including interleukin (IL)-5, IL-13, and eotaxin. Additionally, SO_2 and NO_x levels have been reported to correlate with the daily number of AR patients.[17]

However, it is not clear whether air pollution can cause allergic diseases *de novo*. Birth cohort studies have inconsistent results when comprehensively examined the relationship between early childhood exposure to air pollutants and the development of AR, asthma, and other allergic diseases. A systematic review and meta-analysis of birth cohort studies shows a significant association between early childhood PM2.5 exposure and sensitization to outdoor but not indoor aeroallergens.[18] Based on 5 European birth cohort studies, Gruzieva *et al.*[19] reported no clear association of PM2.5 or PM10 exposure with allergic sensitization in children aged ≤ 10 years.

Inhaled allergens pattern

Since avoiding allergen exposure is key to AR management, identification of allergens is crucial for the diagnosis and treatment of AR. The spectra of inhaled allergens in China are similar to those of Western countries. HDMs, pollen, fungus, animal dander, and cockroaches are the most common aeroallergens,[20,21] among which the 3 most prevalent are from the species *Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farinae* (*Der f*), and *Artemisia.*[21]

HDMs are the major cause of AR in China, especially in Southern China.[22-26] Chen *et al.*[22] generated a distribution map of HDMs and found that the rate and the regional distribution patterns of both *Der p* and *Der f* sensitization were similar in AR patients. *Der p* and *Der f* were the highest in the southern and central parts of China and the lowest in the northern regions, especially in the northwest. Yang *et al.*[25] demonstrated that *Der p* components Der p 1 and Der p 2 could induce *Der p* sensitization in Central China.

Due to high seasonal pollen exposure, which is primarily influenced by local environmental and climate conditions, the prevalence of PiAR is extremely high in Northern China. Most patients with PiAR are sensitive to ≥2 pollens, of which *Artemisia*, *Chenopodium*, and *Humulus scandens* are the most common.[3] In the northern area of the Yangtze River, *Artemisia* pollen is the most allergenic.[27] In Northwest China, the three most prevalent aeroallergens were mugwort, ragweed, and dandelion pollen.[23] Interestingly, there was an increase in pet allergen sensitization from 2005 to 2014.[26] In children, *Der p* was the most common allergen, and the proportion of children with high levels of allergen-specific IgE (sIgE) against *Der p* increased with age.[28] A broader spectrum of allergen sensitization was more common in children than in adults.[21]

MECHANISMS OF IMMUNOTHERAPY

AIT was introduced more than a century ago and is recognized as the only immune-modifying treatment for IgE-mediated airway diseases, such as AR and allergic asthma.

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The mechanisms of AIT are still not fully understood. AIT is based on the administration of gradually increasing amounts of causative allergen extracts, leading to the development of clinical allergen tolerance in atopic patients. Tolerance is accompanied by Th1/Th2 rebalancing, changes in secretory cytokines, production of IgG4 isotype allergen-specific blocking antibodies, induction of regulatory subsets of T and B cells (Tregs and Bregs), and a decrease in inflammatory responses to allergens by effector cells (mast cells, basophils, and eosinophils) and upstream dendritic cells (DCs) in inflamed tissues.[29]

During the last 20 years, Treg cells have been identified to play a pivotal role in inducing and maintaining peripheral immune tolerance. Rebalancing the Th1/Th2 response by altering allergen-specific effector T cells to a regulatory phenotype is a key event during AIT for the development of a healthy immune response to allergens and successful outcome in patients. The immunologic tolerant state following AIT is associated with the induction of distinct phenotypes of Tregs, including IL-10-, IL-35-, and transforming growth factor-β- producing Tregs and $Foxp3^+$ Tregs.[30] In addition to Tregs, other key cell types, such as Bregs and DCs, appear to play important roles in successful AIT.

Desensitization effects following AIT

Both early and late phase allergic responses are suppressed after AIT, starting with the late phase response 2 weeks after commencement of treatment. Most patients start to acquire tolerance against late-phase skin response during the very early phase following AIT.[31] A key mechanistic feature of the early phase reactions is IgE-dependent mast cell and basophil degranulation. High-affinity IgE receptors preferentially bind to free IgE molecules, whereas IgE–allergen immune complexes are cleared upon binding to the low-affinity receptor CD23 on B cells.

Modulation of antigen-presenting cell function following AIT

The second stage in the response is the generation of allergen-specific Tregs and Bregs as well as the suppression of allergen-specific Th2 cells and type 2 innate lymphoid cells.[32] The tolerogenic activity of DCs depends on the maturation status and activation of the cell, in addition to the cell lineage (*e.g.*, myeloid vs. plasmacytoid DCs [pDCs]), all of which can be influenced by immunomodulatory agents. In the absence of pro-inflammatory signals during AIT, airway DCs possess an intermediate phenotype (between immature and mature), expressing a range of co-stimulatory molecules resulting in tolerogenic interaction with lymph-node T cells. Depletion and adoptive transfer of pulmonary pDCs in an asthmatic mouse model showed that pDCs play a central role in protection against sensitization to allergens and the development of asthma.[33]

Modulation of T-cell responses and peripheral T-cell tolerance to allergens following AIT

Active regulation might be an essential mechanism for inducing and maintaining peripheral tolerance to allergens. In allergic diseases, the activities of $CD4^+Foxp3^+$ Tregs, $CD4^+Foxp3^-$ type 1 Tregs (Tr1), and IL-35-inducible Tregs (iTR35) are compromised, and an abnormal Th2 response is observed. However, these abnormal immune responses can be ameliorated by AIT.[34,35] Studies show that Treg and Th1/Th2 responses are normalized during AIT and that there is an upregulation of allergen-specific Tregs and improved clinical response. Moreover, a decrease in the activity and proliferation of allergen-specific follicular helper T cells (Tfh), which contributes to sIgE production, and an increase in follicular regulatory T cells (rTfh) in patients with AR is observed after AIT.[36-38]

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Modulation of antibody responses following AIT

B-cell responses, including the induction of IL-10$^+$ regulatory B cells (Bregs) and the production of IgG4-associated blocking antibodies, are observed after successful AIT. Although allergen-specific antibody responses in healthy control individuals are often undetectable, exposure to high concentrations of allergen can elevate serum levels of allergen-specific IgG4, IgG1, and IgA, but not IgE.[39] *Der-p*-specific IgG (sIgG), sF(ab')2, and sFab antibodies markedly blocked *Der-p*-allergen sIgE complex binding to B cells, inhibited basophil activation, and reduced the production of IL-5, IL-13, IL-17, and tumor necrosis factor-α.[40] Indeed, there is sufficient evidence that functional activity, rather than quantity of IgG antibodies, might be a more appropriate measure of AIT efficacy.

Most recently, a fraction of antigen-specific CD38$^+$ B cells was detected in AR patients.[41] A negative correlation was demonstrated between CD38$^+$ B cell frequency and Treg frequency in AR patients treated with AIT. Exposure to specific antigens induced CD38$^+$ B cells to produce IL-6, which converted Tregs to Th17 cells. Additionally, an increased number of circulating allergen-specific memory B cells and IL-1RA production by Bregs was observed after long-term AIT.

In summary, both innate and adaptive immune responses that contribute to allergic inflammation are suppressed by AIT. Successful AIT is associated with suppression of allergic inflammatory cells and normalization of the Th1/Th2 response. The immunologic tolerant state following AIT is associated with the induction of distinct phenotypes of Tregs and Bregs (**Fig. 1**). Insight into the mechanisms of AIT has allowed identification of novel therapeutic strategies for more effective and safer AIT.

SUBLINGUAL IMMUNOTHERAPY (SLIT) IN CHINA

SLIT is a safer alternative than subcutaneous immunotherapy (SCIT), as it elicits fewer and milder adverse reactions. The first SLIT product, "Chanllergen," a vaccine made with *D. farinae* extract, was approved for the treatment of HDM-induced AR and asthma by the China Food and Drug Administration (CFDA) in 2006.[42] SLIT allows self-administration without the supervision of a physician. Oral intake is allowed 15 min after each treatment. Several Chinese researchers have published the short- and long-term efficacy data of the HDM-SLIT product in both pediatric and adult AR patients.[43-48] The Chinese guideline on SLIT for AR and asthma was published in 2019.[49] The recommended duration of SLIT was 3 years.[45] However, considering the differences in the effectiveness and side effect profiles, individualized treatments are crucial for improving the response rate of SLIT. Recently, Gao *et al.* [50] gave a dosage increase (33.33% for patients < 14 years old and 50% for patients ≥ 14 years old) to low responders (combined symptom and medication score [CSMS] reduction rate ranging from 20% to 50%) after 6 months of SLIT in their clinical study. They found a significant difference in CSMS and visual analog scale (VAS) after 1 year (but not 2 or 3 years) of SLIT between the high responders (CSMS reduction rate over 50%) and low responders (defined after 6 months of SLIT) with a dosage increase. They concluded that a dosage enhancement within a certain range might improve the effectiveness of SLIT. Follow-up is essential for dose adjustments. Thus, beyond the indications and contraindications of SLIT in AR and asthma patients, patient education and follow-up education should also be considered in clinical practice.[49] Poor adherence to SLIT is a major cause of unsatisfactory outcomes for patients with AR. Jin *et al.* [51] evaluated the effect of the length of the first

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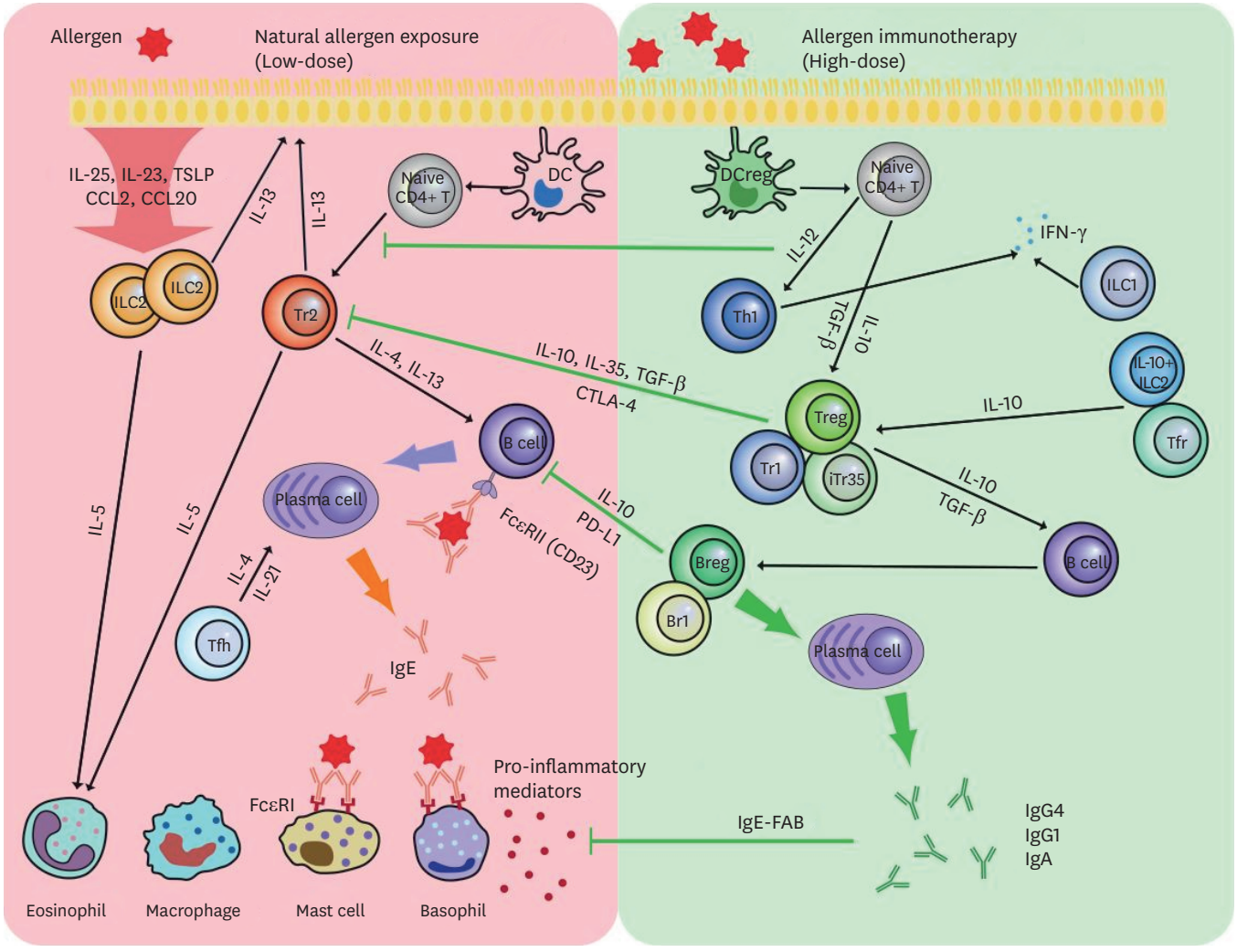

Fig. 1. Mechanisms of immunotherapy.
IL, interleukin; TGF, transforming growth factor; Ig, immunoglobulin.

prescription on the adherence to SLIT. Here, > 6 months for the first prescription gained the best adherence (86.05%) rate compared with < 3 months (58.82%) and between 3 and 6 months (30.43%). Meanwhile, Gao *et al.* [50] also reported that 6 months might be a critical time point for efficacy assessment and dosage adjustment for SLIT-treated AR patients. Presently, there is no recommended dose adjustment regimen or length of the first prescription for SLIT. More research on individualized treatment and adherence improvement is needed to improve the effectiveness of SILT.

Artemisia pollen allergy is a unique local issue affecting a large number of individuals in Northern China. Recently (May 2021), *Artemisia annua* allergen SLIT drops, the first standardized pollen allergen extracts in China, were approved by the CFDA for clinical use in seasonal AR patients. In a phase 3, multicenter, randomized controlled trial (RCT) (registered at clinicaltrial.gov as NCT03990272) conducted by Lou *et al.*,[52] 702 *A.-annua*-sensitized patients were randomized to receive *A.-annua*-SLIT or placebo. Mean daily CSMS was significantly improved during the peak pollen period in the SLIT group compared with the placebo group, 1.46 ± 0.47 vs 1.88 ± 0.42, $P < 0.0001$ in the full analysis set and

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1.49 ± 0.52 vs. 1.95 ± 0.46, $P < 0.0001$ in the per protocol set, representing a 22.3% and 23.6% reduction relative to placebo, respectively. *A. annua* SLIT was well tolerated, with no deaths, drug-related serious allergic reactions, anaphylaxis, or life-threatening events during treatment. The percentage of participants reporting adverse events (AEs) was 91.5% (410/448 in the *A. annua* SLIT group and 205/224 in the control group). Most AEs were early-onset, transient, self-limiting reactions, with oral paresthesia the most common drug-related AE in the *A. annua* SLIT group (36.8%). The results of a post-marketing study showed an equivalent efficacy and safety for seasonal AR patients accepting a pre-seasonal treatment of 8–9 or 12–13 weeks, regardless of monosensitization or polysensitization. More post-marketing studies are needed to evaluate the cost-effectiveness and safety of this newly launched SLIT product.[53]

Currently, only the 2 above-mentioned standard allergen extracts are available for SLIT in China. Products for the management of other clinically relevant allergens are urgently needed.

NOVEL ROUTES OF ADMINISTRATION OF AIT

Apart from the well-proved conventional treatments, SCIT and SLIT, some novel routes with relatively short durations, such as intralymphatic immunotherapy (ILIT), epicutaneous immunotherapy (EPIT), and intradermal immunotherapy (IDIT), are understudied.

ILIT

Based on the "geographic concept of immunogenicity," ILIT directly delivers the allergen to B and T cells in the lymph nodes and is reported to induce a more robust cytotoxic T-cell response than other routes.[54] The inguinal lymph nodes are the most common injection sites for ILITs.[55,56] Considering the inconvenience of inguinal ILIT injection, Wang *et al.*[55] conducted a first-in-human cervical ILIT study. No moderate–severe AEs were observed. The advantages of ILIT over conventional treatments are the shorter treatment duration and fewer injections. The current protocols for ILIT suggest 3 injections at 4-week intervals, which could be completed over 8 weeks.[55,57-63] Beyond convenience, ILIT has shown promising safety and tolerance. Senti *et al.*[57] compared ILIT with SCIT (n = 58 vs. n = 54) and demonstrated that ILIT had fewer AEs. The pain of intralymphatic injection was reported as the most frequent AE.[64] Park *et al.*[65] further compared the injection pain of ILIT with venous punctures during blood sampling. They reported that the pain caused by intralymphatic allergen injection was more intense (VAS score: 3.5 ± 2.0 vs. 2.8 ± 1.7 mm, $P = 0.019$), but not different from that of intralymphatic placebo injection. Sixteen studies (14 RCT[55,57-60,62-70] and 2 cohort studies[61,71]) provided data on anaphylaxis and death; among the 1,454 injections, 4 anaphylaxis events and no deaths were reported.

Efficacy evaluations of ILIT have shown inconsistent results, possibly due to the variation in allergen extracts, dosages, and administration intervals. Some studies showed no clinical benefit of ILIT for perennial AR.[55,58,61] However, Park *et al.*[65] reported that ILIT reduced daily medication use and skin reactivity to HDM and cat allergens 4 months after treatment. For seasonal AR, a meta-analysis showed short-term (< 24 weeks) benefits on CSMS in the 4-week, but not the 2-week, injection interval subgroup.[54] The medium-term (24–52 weeks) benefits of seasonal AR symptom VAS scores favored ILIT when analyzing data from 4 RCTs (mean difference, 1.93; 95% CI, 0.92–2.94; $P < 0.01$).[54] Skaarup *et al.*[66] reported no long-term (> 52 weeks) effect of ILIT on CSMS compared with placebo; Terada *et al.*[67] also found no

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long-term effect of ILIT using VAS scores for the evaluation of clinical benefit. The dosages were fixed in most studies, whereas 3 used escalating doses.[58,60,70]

ILIT requires only 3 injections over 8 weeks, and the cumulative dose is 1/1,000 of a 3-year SCIT. Compared to the conventional AIT routes, ILIT is quicker and reduces the number of clinical visits and costs. Importantly, although the safety and tolerability of ILITs is proven, the effectiveness of ILIT should not be overstated due to the discordance in efficacy evaluations. No recommended dose could be concluded from the published studies and escalating dosages may increase the risk of anaphylactic reactions.[70] A preseason booster dose was assessed in 3 studies, Konradsen *et al.*[63] and Weinfeld *et al.*[71] showed clinical improvement, whereas Skaarup *et al.*[66] reported no additional effects of the preseason booster. Dose-range studies regarding effectiveness using established allergens (grass pollen, birch pollen, and mountain cedar pollen) and studies with a larger sample size, consistent efficacy indicators, and long-term follow-up periods are needed.

EPIT

EPIT delivers allergens via repeated applications to the skin, targeting epidermal Langerhans cells; it can reduce both local and systemic AEs. First used over a century ago, the disruption of the skin has evolved from "skin scarification" to the commonly used "tape stripping."[72] Although the tape-stripping method increased the penetration of allergens into the epidermis, it provoked similar Th2 immune responses and allergic sensitization to scarification.[73] Senti *et al.*[74] conducted 3 studies with grass pollen applied on patches after repeatedly tape-stripping the skin. Six patches were given preseason at weekly intervals and self-applied onto the tape-stripped skin of 98 subjects. EPIT produced a median symptom improvement of 48% after treatment and 40% in the treatment-free follow-up year compared to a 10% and 15% improvement after placebo EPIT, respectively (allergen extract: n = 48; placebo: n = 50, $P = 0.003$). Furthermore, sIgG4 responses were significantly elevated ($P < 0.001$) in the allergen EPIT group, but not in the placebo group. One systemic reaction (SR) was reported by a patient after tape stripping, but before application of the patch. Local side effects were associated with the duration of patch administration. EPIT efficacy was dose-dependent, and a high dose was associated with local skin inflammation.[75]

Several innovative epidermal powder delivery systems are understudied, including electronic spreading (Viaskin™), laser-based microporation, and microneedle arrays.[76] Powder-laden dissolvable microneedle array (PLD-MNA) is reported to have a higher powder delivery rate than Viaskin. Additionally, various lyophilized extracts of allergens that are available for skin prick tests (SPTs) can also be directly loaded into PLD-MNAs. PLD-MNAs should be used in clinical trials. Future investigations into EPITs seem promising.

IDIT

Slovick *et al.*[77] reported in 2017 that IDIT with the major timothy allergen, Phl-p 5, was associated with worse nasal and asthma symptoms during the grass pollen season, although it did reduce allergen-specific late-phase cutaneous reactions compared with the histamine control. IDIT also increased Phl-p-5-specific serum IgE and led to higher expression of Th2 and lower expression of Th1 on the surface of T cells cultured from skin biopsy specimens. A multicenter, placebo-controlled RCT study in Spain confirmed that in patients with grass PiAR, IDIT with glutaraldehyde-polymerized *Phleum pratense* was effective and safe. During the pollen season for 2 consecutive years, 6 injections/year were administered. In the second pollen season, the level of sIgE was decreased whereas IgG4 was comparable to baseline.[78] Skillful medical workers are required to administer IDIT.

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In summary, using novel routes of administration has dramatically reduced the number of treatments required compared to conventional AIT. Although the safety and tolerability of these novel routes were acceptable, only ILIT and EPIT seem promising in terms of efficacy. Even then, this effectiveness is only shown for seasonal AR patients. Considering the comparatively limited number of patients in ILIT clinical trials, the efficacy and safety of ILIT need confirmation. Further dose-range studies, especially with allergens beyond seasonal pollen, are also required.

ALLERGEN VACCINES

Successful allergen-specific immunotherapy depends on high-quality allergen vaccines or extracts.[79] Allergen extract is an allergen preparation extracted from natural source materials, such as mites, pollens, and animal dander. They mainly contain active substances, such as proteins or glycoproteins, and non-allergenic molecules. These active substances are allergens that are able to elicit an IgE response in the human immune system.[80] There are certain differences between allergy vaccines from different companies, and variations between batches produced by a specific manufacturer depending on the quality and purity of the raw materials, methods of extraction, and representation of the individual allergen molecules and their immunogenicity.[80,81] Standardization is thus a prerequisite for controlling variability in specific immunotherapy for allergic diseases.[81]

Similar to European counties,[79] there are no certified references for allergen standardization in China. In-house reference (IHR), characterized using several *in vitro* methods, is used for standardization by individual manufacturers[82] and labeled in manufacturer-specific units. Each batch of allergen product is compared to the respective IHR. The total biological potency of allergen products is generally determined using *in vivo* methods. Subsequent batches of allergen extract are compared with the IHR, and thus the *in vivo* method is not necessary for batch-to-batch standardization.[83] Currently, only HDM[84] and *A. annua*[52,85] allergen extracts are authorized for specific immunotherapy in China.

Der p and *Der f* are the most common allergen sources for allergy patients in China[24] and found in most beddings in the country.[86] HDM allergen extracts are produced as aqueous, glycerinated, and aluminum-precipitated formulations. Standardized products are labeled as a biological unit.[87,88] The units currently appearing on labels of marketed products are: SQ-U (Standardized Quality-Units)/mL, TU (Therapeutic Units), and HEP (Histamine-Equivalent Prick testing). Non-standardized allergen extracts are labeled as wt/vol, which indicates weight in grams per volume in milliliters. Extracts with a particular wt/vol may have a wide variability in biological potency.[89,90]

The National Medical Products Administration (NMPA) of China stipulates quality control requirements for allergen vaccines, including total protein content, protein composition, major allergen content, and total allergenic potency. All allergen products in China should be characterized based on these criteria.

In contrast to allergen extract from natural sources, recombinant allergens are generated using recombinant DNA technology, and the quality depends on the cell lines used, fermentation processes, and purification procedures. Recombinant allergens consist of predefined allergenic polypeptides. The quantity and structure of the polypeptides used in

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recombinant allergens should be determined. Recombinant allergens from *Der f* have been investigated intensively in China.[91-99] The NMPA has yet to publish quality control guidelines for recombinant allergens, and no product has been authorized.

In summary, standardization is necessary for ensuring the consistency and reproducibility of allergen products for safety and effective disease management. However, there is no uniform standardization system in China or the quality of allergenic products available in the market varies significantly. Therefore, it is recommended that only products with specified total potency and concentrations of individual allergens be used for AIT.

DIAGNOSTIC AND DIFFERENTIAL DIAGNOSTIC METHODS

SPTs

SPTs are widely used for rapid detection of IgE-mediated allergic reactions *in vivo* because of their simplicity, sensitivity, and low cost. They demonstrate high sensitivity and specificity during the diagnosis of inhalant allergens.[100]

Importantly, SPTs should be standardized, and operators should receive pre-job training and obtain qualifying certifications. Standardized allergen extracts (prick fluid), negative control (saline/glycerin), and positive control (5–10 mg/mL histamine solution) are required for SPTs. Wheal or erythema is measured approximately 15–20 minutes after pricking the extracts into the skin in patients and 20 minutes to 24 hours, in patients with delayed skin reactions. Unilateral or bilateral forearms are routinely used for the test, but the back can also be used, especially in infants. Wheal diameters ≥ 3 mm are considered a positive reaction,[101] and the red blush can be used as a reference. Metal single-point pricks are recommended in SPTs,[102] and the skin index (SI) is often used to assess SPT results. The SI is the ratio of average diameter of wheal to positive control, and determined according to 4 grades: +, 0.3 ≤ SI < 0.5; ++, 0.5 ≤ SI < 1.0; +++, 1.0 ≤ SI < 2.0; and ++++, SI ≥ 2.0.

Clinical studies show that the 8 most common types of aeroallergen cover 95%–99% of allergic patients.[103] Since the only NMPA-approved allergens in China are from HDMs, the clinical application of SPTs in China is greatly restricted.

SPTs can be performed in infancy, but the responsiveness is very low.[104] However, children's responsiveness to SPTs increases with age and continues until adulthood before gradually declining.[105]

Notably, it is important to consider the patient's clinical symptoms and medication history when interpreting SPTs results. False-positive skin tests can result from dermographism or a nonspecific enhancement from a nearby strong positive reaction. False-negative skin tests may be caused by poor potency extracts (reagent), modulation of allergic reactions by drugs, or inadequate prick force.[106]

Serum allergen sIgE tests

The primary purpose of an allergen test is to identify the causative allergens (usually allergen proteins) that cause allergic diseases. Since 1967,[107] the serological allergen sIgE test has been regarded as an effective diagnostic method for human allergic disease. Serological sIgE tests are not as affected as SPTs by factors such as age, drug usage, and dermatographism, and

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are especially effective for false-negative SPT individuals. Qualitative, semi-quantitative, and quantitative IgE antibody immunoassays are currently available. The full-quantitative detection of physiological levels of total and sIgE is important for patient management and monitoring of therapeutic interventions, such as anti-IgE therapies. Quantitative system results are generally reported in international units (kU/L [serum total IgE assays] or kUA/L [serum sIgE antibody assays]).[108] Historically, patients with sIgE concentrations ≥ 0.35 kUA/L were considered positive. However, recently it was proposed that IgE antibody tests d be reported as analytical results and not based on differential positive or negative thresholds. Additionally, it was proposed that the lower limit of quantitation for autoanalyzer-based IgE assays be 0.1 kUA/L.[109] However, IgE antibody levels between 0.1 and 0.35 kUA/L must be cautiously interpreted by clinicians and should be combined with the actual symptoms after allergen exposure.[110] This should be given considerable attention when the sIgE result is employed to distinguish between sensitization and allergy at all concentrations, *i.e.*, an sIgE positive result alone, without allergic symptoms, is insufficient for a definitive diagnosis of allergy.

Nasal cytology is a simple, non-invasive, economical method of assessing pathological aspects of nasal mucosa.[111,112] It is a useful auxiliary method for the diagnosis and prognosis of AR. There are various techniques to obtain specimens for nasal cytology, such as nasal lavage, pre-weighted sinus packs, aspiration by micro-suction tubes, nasal brushing, nasal scraping, nasal swab, nasal smear, and nasal biopsy,[112,113] and this is followed by sample staining and microscopy. At least 50 fields should be evaluated at 1,000× magnification. The counts of epithelial cells, mucinous cells, lymphocytes, neutrophils, eosinophils, and mast cells can be expressed as a percentage of the total cells, an absolute quantity, or by a semi-quantitative grading.[111,112]

Eosinophil number is regarded as an important marker for atopic reaction.[114] In various studies, the nasal cytological examination of eosinophils appears to be an auxiliary diagnostic tool with moderate sensitivity and high specificity in AR diagnosis.[115] Although a nasal cytological test of eosinophils is not necessary for the routine diagnosis of AR, it is often introduced as a useful differential diagnostic method for AR and other subtypes of non-allergic rhinitis in the clinic. Eosinophil or neutrophil dominated inflammation is reported if the ratio of eosinophils or neutrophils is more than 20% of the total inflammatory cells.[112] Mast cell degranulation is graded as follows: 1, mild granules; 2, a moderate number of granules; 3, many granules; and 4, massive degranulation.[112] Furthermore, eosinophilia correlates significantly with clinical parameters and nasal atopic reaction in AR patients.[116] The cytological measurement of other cells, such as mast cells, basophils, neutrophils, goblet cells, and epithelial cells, may provide useful information for the differential diagnosis and management of AR. A study reported differences in the percentages of epithelial cells and neutrophils in the nasal cavity of perennial and intermittent AR patients.[117] Moreover, a recent publication demonstrated that inhibiting neutrophil proliferation and activity is important in AR patients with high nasal neutrophil counts.[113] Nasal cytology may have the potential to identify subtypes of AR for effective treatments.

Huggins and Brostoff[118] demonstrated, for the first time, that sIgE could be detected in nasal secretions from AR patients. In a mouse model, prolonged low-dose allergen exposure in the sensitization phase could induce localized sIgE and prominent accumulation of eosinophils in nasal mucosa without detectable levels of serum sIgE.[119] Several studies have since demonstrated local production of IgE antibodies in the nasal secretion and nasal mucosa of AR patients, leading to the concept of "entopy."[120] To date, local sIgE is used not

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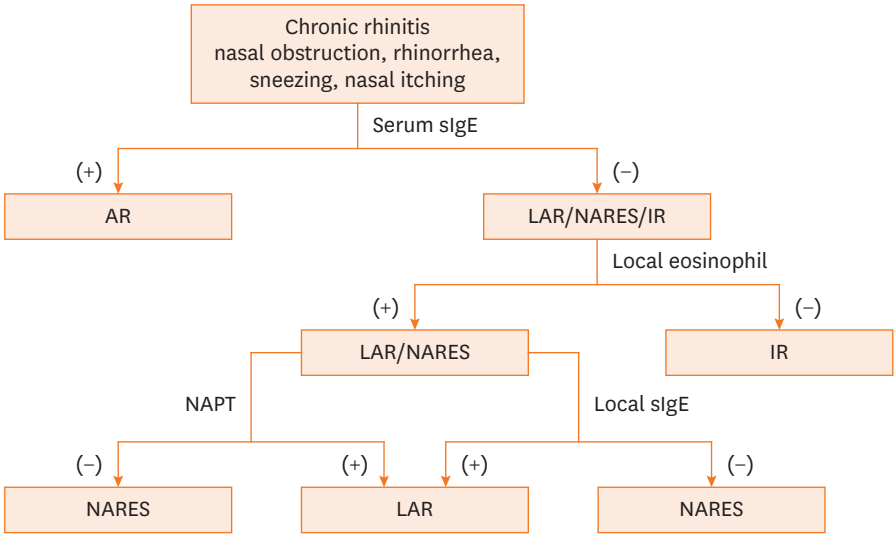

Fig. 2. Stages for the diagnosis of different chronic rhinitis endotypes.
Ig, immunoglobulin; AR, allergic rhinitis; LAR, local allergic rhinitis; NARES, nonallergic rhinitis with eosinophilia syndrome; IR, idiopathic rhinitis; NAPT, nasal allergen provocation test.

only for endotype diagnosis of chronic rhinitis[121] but also for precise diagnosis of AR. In a study involving 51 rhinitis patients, it was observed that the sIgE level in nasal secretions could be a reliable non-invasive alternative to serum sIgE for diagnosis.[122] Additionally, a new type of rhinitis, local AR (LAR) was discovered using local sIgE, with a 7.7% prevalence in Southern China. Pollen was the most common sensitizing allergen for LAR among patients, differing from results in Caucasians where HDM was the dominant sensitizing allergen. Monosensitization was the predominant pattern in Chinese LAR patients.[123] Additionally, the nasal allergen provocation test (NAPT) was reported as the most effective method for the diagnosis of LAR. However, NAPT has several limitations in clinical practice, including the absence of standardized methods and some reagents, the presence of several test protocols, the need for trained personnel, and difficulties in performing on pediatric patients. In a prospective single-center study involving 212 chronic rhinitis patients, local sIgE levels in nasal secretions were reliable and effective for diagnosing LAR (**Fig. 2**).[124]

PATIENT SELECTION

Indication and contraindication

Indication

AIT is recommended for AR patients with obvious allergen-related symptoms. Identification of clinically relevant allergens via SPT or serum sIgE is the first step of patient stratification to ensure that the correct allergen agent is used for AIT. NAPT is helpful in confirming clinically relevant allergens before the initiation of AIT.[125] However, there is no standardized commercial product for NAPT currently available in China.

Since AIT is the only available etiological treatment that can modify immune system status with long-term efficacy for AR,[126,127] it is recommended as the first-line treatment and initiated early in the course of the disease. However, considering the time duration and costs, AIT is especially recommended for patients under the following conditions: 1)

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inability of pharmacotherapy (antihistamines, anti-leukotrienes drugs, nasal glucocorticoids, *etc*.) to effectively control the symptoms; 2) presence of serious adverse reactions during pharmacotherapy; 3) patients' reluctance to undergo continuous or long-term pharmacotherapy; and 4) patients' desire for the long-term advantages of AIT.[128]

Since patient compliance is pivotal for the success of immunotherapy and is also an important factor avoiding adverse reactions, the following factors should be considered when AIT is recommended: 1) patients' preference and compliance; 2) convenience of treatment; 3) severity of symptoms and effect of drug treatment; and 4) effects and possibility of allergen avoidance.[129] Before initiating AIT, good communication with patients is essential. Patients must be informed of the following items: the practical procedure, the duration of treatment, the expected effects, and the potential risks.

The indication for SLIT is similar to that for SCIT. The failure of pharmacological treatment is not an essential prerequisite for the use of SLIT. SLIT is now widely used in China as it is non-invasive, safe, and probably self-administered at home. It is a more acceptable option for some patients with concerns about adverse reactions, objections to repeated injections, and inconvenient frequent hospital visits, especially during the COVID-19 pandemic.

Contraindications

The decision to use SCIT in patients with contraindications or concomitant diseases is usually based on the risk-benefit balance. In individual cases, SCIT may be a treatment option when the expected benefit is greater than the potential risk. This information is required by clinicians to determine whether patients have relevant absolute or relative contraindications, which could result in the risk of SCIT exceeding the expected benefits (**Table 1**).[1,130-132]

Special considerations in immunotherapy

HDM allergens are the most relevant allergens in AR during childhood.[24] AIT is one of the most useful methods for treating respiratory diseases due to HDM allergy. AIT products are commercially available for SCIT or SLIT administration. Alternative routes, such as intralymphatic or epicutaneous administration, have not been tested in a pediatric population.[132]

Table 1. Contraindications to SCIT

Consider the following factors	Introduction
Age	Children < 5 yr of age and older adults > 65 yr of age are absolute contraindications.
Drug use	The use of beta-blockers, ACE-inhibitors, immunosuppressive agents, and anti-cancer drugs.
Asthma	Unstable asthma (uncontrolled or severe asthma) is an absolute contraindication.
Malignancy	Active malignant neoplasia is a contraindication.
Cardiovascular disease	SCIT should be carefully selected based on the patient's ability to tolerate anaphylaxis episodes in case of unstable angina recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.
Pregnancy	Do not commence SCIT during pregnancy. If SCIT treatment before pregnancy is well tolerated, it can be continued during pregnancy or breast-feeding.
Immunodeficiency or autoimmune diseases	HIV is a relative contraindication; uncontrolled systemic autoimmune disease is an absolute contraindication. Primary and secondary immunodeficiencies are relative contraindications.
Adherence	Psychosis and mental disorders are relative contraindications, which raises the questions of compliance and cooperation.
Atopic eczema	Severe atopic eczema is a relative contraindication.
Anaphylaxis to SCIT	History of severe systemic reactions to SCIT is a relative contraindication.

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Concerning AIT, children belong to a so-called special population. Age and safety are important factors for considering when initiating AIT in children. Although the clinical efficacy of AIT in AR is well established, children > 3 years old are seldom involved in clinical practice or trials. For safety reasons, it has been established by expert consensus that AIT can only be applied to children at ≥ 5 years old. However, AIT can be considered in children < 5 years old on an individual basis. Several factors should be considered, such as the impact on quality of life, expected acceptance, and adherence to the AIT. Attending physicians should communicate effectively with patients and their families regarding the practicalities, benefits, risks, and contraindications such as uncontrolled asthma.

In terms of indications, AIT is currently recommended in children with moderate-to-severe AR[132] and should be initiated as early as possible for optimal results. Children with AR who are nonresponsive to standard pharmacotherapy should be considered for AIT.

Several published studies have examined the efficacy and safety of AIT.[133-137] Moreover, evidence has shown that AIT could reduce symptoms and medication use. Additionally, a controlled trial of pollen immunotherapy in children suffering from seasonal AR revealed that significantly fewer SCIT-treated subjects had developed asthma at a 10-year follow-up.[133] These studies provide evidence that SCIT may reduce the onset of new allergen sensitization in children.[134,135] Currently, there is modest evidence for the clinical efficacy of continuous SCIT in children suffering from seasonal AR to grass pollen and perennial AR to HDMs,[136] and there is no evidence suggesting that AIT can worsen eczema or induce more frequent exacerbations. A comparative study of SCIT and SLIT showed that local AEs were reported in both SCIT- and SLIT-treated children, with similar numbers seen in the placebo group.[136] In a recent large-scale study, a total of 19699 SCIT and 131550 SLIT doses were administered; the estimated frequency of systemic side effects with SCIT and SLIT was 0.11% and 0.004%, respectively, and the probability of abscission due to adverse reactions was similar between the two treatments.[137] Overall, studies have shown that both SCIT and SLIT are safe and well-tolerated treatments in children with AR.

Currently available data suggest that AIT (SCIT and SLIT) should be used for at least 3 years in children to achieve significant clinical efficacy.[132]

AIT during pregnancy

AR constitutes a significant disease burden among women of childbearing age and pregnant women. AIT has also been considered for use during pregnancy. A review on the safety of AIT during pregnancy showed that there was no significant difference in maternal or fetal complications in pregnant women using AIT (both SCIT and SLIT to inhalant allergens) compared to the control group. Among some pregnant women (10/453 pregnancies) who experienced generalized reactions while receiving AIT, none were found to have fetal complications. Neither SCIT nor SLIT during pregnancy altered the risk of developing atopic disease in the offspring.[138] According to the European Academy of Allergy and Clinical Immunology (EAACI), AIT may be continued during pregnancy[139]; however, data regarding the safety of continuing AIT during pregnancy is presently lacking in China. In China, before initiating AIT, it is usually verified if the patient has a plan for pregnancy in the near future. However, proper patient education is necessary for informing patients of the possible risks, benefits, and safety of AIT during pregnancy. Some data suggest that the initiation of AIT during pregnancy might be safe.[140,141] However, given the limitations of the medical environment in China, commencing AIT during pregnancy is not recommended.

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ADMINISTRATION OF IMMUNOTHERAPY CENTER

Training of immunotherapy personnel

1. Due to the COVID-19 pandemic, there have been considerable changes in the procedure of AIT and its related medical risks. These changes emphasize the need for training SCIT managers in the post-pandemic era.[142] However, the responsibilities of SCIT personnel during the pandemic are as follows.

- Follow basic medical norms in the diagnosis and treatment activities.
- Ensure compliance with SCIT standard operating procedures.
- Follow COVID-19 prevention measures to ensure safe diagnosis and treatment of patients receiving SCIT during the pandemic.
- Ensure that the patients' adverse reactions, including anaphylactic shock during SCIT, are attended to in a timely manner.
- In compliance with COVID-19 prevention regulations, ensure that patients receiving SCIT undergo timely follow-up, and ensure the continuity of SCIT treatment.
- Accurately identify risks associated with SCIT-related diagnosis and treatment activities during the pandemic to ensure the safety of these activities.

2. To ensure the development and operation of SCIT during the pandemic, we recommend training medical personnel and patients. The training content for medical personnel should include the following:

- Basic medical standard training on the intractable case discussion system for allergic diseases, such as immunotherapy for patients with multiple allergic diseases; the patient medical record management system; the prescription management system; prevention and handing of medical treatment accidents; nosocomial infection prevention and control system; and the verification system during subcutaneous injections.
- SCIT operation process training, including evaluation of patients' condition (including clinical symptoms and peak respiratory flow meter testing) to determine whether injection can be started or continued at the current dose (parents of children <15 years old must participate in the evaluation of this project); accurate and updated data for each patient during immunotherapy; standardized injection techniques; dose adjustment during treatment; strict observation of patients' condition (including pediatric patients); early detection of adverse reactions; treatment and monitoring of patients with adverse reactions; regular review and evaluation of treatment procedures; and evaluation of factors that could affect the continuation or termination of treatment.
- Proficiency in the treatment of adverse reactions to immunotherapy and the standard operating process of cardiopulmonary resuscitation. Notably, each center should conduct yearly anaphylactic shock rescue training, including emergency procedures and the correct use of emergency rescue equipment. Training records should be kept. Medical personnel must receive cardiopulmonary resuscitation skills training before commencing the job and should be familiar with operating techniques, including cardiopulmonary resuscitation, endotracheal intubation, and the use of artificial resuscitation balloons, sputum suction, oxygen inhalation, and aerosol inhalation. Medical personnel should be proficient in the rescue procedures for anaphylactic shock. Cardiopulmonary resuscitation techniques training should be conducted once a year. Additionally, the hospital should be responsible for spot checks, result recording, and unified management.
- Training of AIT personnel on the COVID-19 response process during the pandemic, including response planning in high-risk areas; the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) nucleic acid testing plan; the home isolation system in

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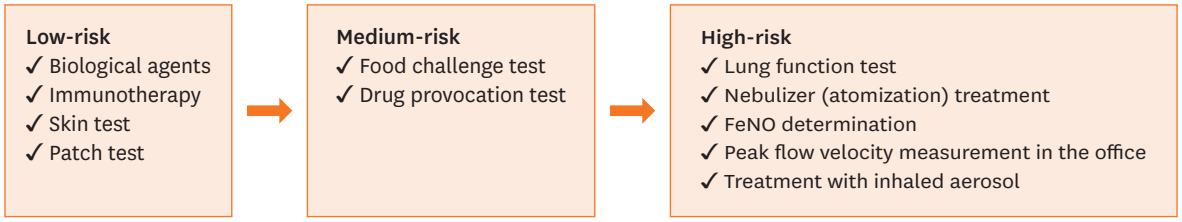

Fig. 3. Risk levels of allergen-immunotherapy-related diagnosis and treatment activities during the pandemic. FeNO, fractional exhaled nitric oxide.

emergency situations; and the interactions, intervals, and precautions of vaccination, combined with SCIT.[143]

- Personal protection training during the pandemic, such as hand hygiene measures and the use of personal protective equipment including facemasks.
- Emergency plan training including emergency personnel plan for absenteeism caused by the COVID-19 pandemic.[144]
- AIT patient follow-up training, including AIT electronic follow-up system training, telephone follow-up and patient appointments, and a long-term follow-up system for particular patients such as those with severe adverse reactions.
- AIT center patient protection process or system training during the pandemic, such as system training for patient triage, guidance, and limits on the number of patients during the pandemic.
- Risk identification training for AIT-related diagnosis and treatment activities during the pandemic such as high-risk diagnosis and treatment activities (**Fig. 3**). It is recommended that medical personnel use personal protection, including protective clothing, gloves, goggles, masks, N95 respirators, and shoe covers.[142] After operations are completed, the room must be cleaned thoroughly. It is recommended that medium-risk diagnosis and treatment activities be conducted when medical safety can be guaranteed (with the presence of emergency rescue facilities, personnel, and institutional regulations).

3. Patient education and training are also an important part of the AIT process. To ensure effective and safe diagnosis, and effective AIT treatment during the pandemic, it is recommended that patient training include the following:

- Basic knowledge on the prevention and treatment of COVID-19 including the source of infection and transmission routes, common symptoms and signs, treatment procedures, and preventive measures.
- Immunotherapy process training during the pandemic such as the visit registration and health code presentation process.
- Training on personal protective measures, including correct face mask usage; social etiquette, such as maintaining a social distance of more than 1 m between people; and vaccination.
- Placement of signs or posters at entrances, bathrooms, and important locations in outpatient clinics to provide instructions on hand hygiene, respiratory system hygiene, and cough etiquette.
- Encouraging patients to maintain good communication with medical personnel via the department hotline or hotline for COVID-19-related issues.
- Training patients receiving AIT on medication and self-monitoring of symptoms at home (such as home quarantine).
- Training on appropriate vaccination intervals for COVID-19[145] and other vaccines[146] during AIT (**Table 2**).

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Table 2. Suggested intervals for vaccination during AIT

Vaccines	SCIT	SLIT	Other routes of AIT administration
COVID-19 vaccine	1 week interval	(1) 3–7 day interval (vaccination before SLIT) (2) Vaccination on the same day is not recommended; vaccination should be postponed by 1 day (vaccination after SLIT)	An interval of 7–14 days
Other vaccines	Follow the package insert/manufacturer's recommendations		

AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; COVID-19, coronavirus disease 2019.

Management and follow-up of patients

Treatment of AIT patients comprises that in-hospital and out-of-hospital managements. The former involves electronic or hard-copy medical records, whereas the latter mainly involves patient follow-up in the form of telephone calls and SMS messages. Patient follow-up includes education on allergic diseases and telephone reminders of treatment schedules.

In-hospital management

Signed informed consent form: patients should be educated on the importance of informed consent, which should be obtained from the patient before commencing AIT. Additionally, patients should be sufficiently educated on AIT.

Data entering into the database: general patient information, clinical diagnosis, and changes in symptoms and signs during AIT.

Paper injection record form: information that includes peak expiratory flow (PEF) before each injection, general condition evaluation, and local and SR 30 minutes after injection.

AIT follow-up card: This card informs patients of treatment precautions and contains contact telephone numbers. The next injection time and the medication status of patients are also recorded on the AIT follow-up card.

Out-of-hospital management and follow-up

Various forms could be adopted for out-of-hospital management and follow-up. The outpatient department can distribute pamphlets and publications to improve patients' knowledge of diseases, including causes and prevention. Additionally, patients can receive medical consultations via telephone, WeChat, and the hospital website. Furthermore, follow-up should be conducted regularly and health care professionals should be willing to satisfactorily respond to a variety of AIT-related questions from the patient.

A lack of patient education is a major cause for poor compliance among patients receiving AIT. The main causes for poor adherence were adverse reactions, inconvenience, and lack of efficacy. Other factors have been associated with poor adherence, such as age and the patient's educational level.[147] Therefore, AIT should be combined with proper management. Patients should be educated about the nature of the allergic disease, disease progression, and the need for treatment.[132] Patient education and effective doctor–patient communication are important for optimal treatment outcomes.

IMMUNOTHERAPY SCHEDULES AND DOSES

Conventional immunotherapy

Presently, the only NMPA-approved SCIT vaccines in China are standardized allergen extracts

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of mite allergen, Novo Helisen-Depot (NHD) (Allergopharma GmbH & Co. KG, Germany; approved in 1999) and Mites allergens ALK (503) *Der p* (ALK-Abello A/S, Denmark; NMPA approved in 2004).[7] Both vaccines are now widely used. There have been several studies on the long-term therapeutic effects of SCIT with standardized HDM allergens in AR patients in China.[148-152] SCIT includes the initial and treatment phases. SCIT involves initial exposure to a diluted concentration of antigen as determined by the safe starting dose or the "end-point" from quantitative testing.[153] This is followed by the escalation phase, in which the dose is gradually increased on a regular schedule to a therapeutic dose that treats symptoms without causing unacceptable reactions.[154] The final phase is the maintenance phase, which is maintained for 3–5 years.

Initial schedules

The initial dose for immunotherapy is dependent on the allergy testing method. Immunotherapy is initiated when the symptoms are as mild as possible and treatment is always started with the lowest dose. The vaccine is usually injected weekly during the initial treatment stage, which usually lasts for 15 weeks (**Table 1**). When treating highly sensitive patients, specific immunotherapy is carried out in accordance with the "highly sensitive" dosage guidelines.

Maintenance schedules

The maximum tolerated dose at the initial stage is the maintenance dose, which is 100,000 standard quality (SQ) units, equivalent to Vial No. 4 (1 mL). After reaching the maintenance dose, the first injection is administered every 2 weeks; the second is administered 4 weeks later; and the third is administered 4–8 weeks after that (as determined by the clinicians). This is followed by subsequent administrations (**Table 3**). The maintenance dose is then injected every 4–8 weeks for 3–5 years.

Table 3. Conventional immunotherapy schedules

Schedule	Week	Injection No.	Vial No.	Capacity (mL)	Concentration (SQ-U/mL)	Dose SQ units
Initial	1	1	1	0.2	100	20
	2	2	1	0.4	100	40
	3	3	1	0.8	100	80
	4	4	2	0.2	1,000	200
	5	5	2	0.4	1,000	400
	6	6	2	0.8	1,000	800
	7	7	3	0.2	10,000	2,000
	8	8	3	0.4	10,000	4,000
	9	9	3	0.8	10,000	8,000
	10	10	4	0.1	100,000	10,000
	11	11	4	0.2	100,000	20,000
	12	12	4	0.4	100,000	40,000
	13	13	4	0.6	100,000	60,000
	14	14	4	0.8	100,000	80,000
	15	15	4	1.0	100,000	100,000
Maintenance	17	16	4	1.0	100,000	100,000
	21	17	4	1.0	100,000	100,000
	27	18	4	1.0	100,000	100,000
	33	19	4	1.0	100,000	100,000
	39	20	4	1.0	100,000	100,000
	45	21	4	1.0	100,000	100,000
	51	22	4	1.0	100,000	100,000

SQ, standard quality.

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Cluster schedules

Generally, SCIT is composed of 2 phases: a build-up phase and a maintenance phase.[132] Conventional SCIT procedure consists of weekly injections for 15 weeks and maintenance injections every 4 or 8 weeks for 3 years.[155] To improve long-term compliance and reduce the number of patient visits, cluster or rush schedules have been developed, which involve shortening the build-up phase by administering multiple injections at the same visit to reach the maintenance dose within a shorter time than the conventional schedule. However, the safety of this schedule is of considerable concern. A meta-analysis of 5 observational studies and 6 interventional studies demonstrated that the cluster schedule was safe for AR patients with or without asthma.[156] Moreover, studies have shown that the cluster schedule contributes to more rapid symptomatic improvement (6 weeks earlier than with the conventional SCIT schedule), without increasing systemic adverse effects (0.15% of injections).[155,157] The most widely accepted cluster schedule targeting HDMs involves injecting the extracts 14 times within 7 weeks in the build-up phase. This schedule was included in the Chinese guideline on AIT in 2017.[158] Apart from SCITs targeting HDMs, several cluster schedules targeting grass pollen[159,160] and venom[161] have been developed.

Rush schedules

Rush immunotherapy (RIT) is one of the methods for accelerated AIT. Its purpose is to shorten the dose-accelerating stage and reach the dose maintenance stage faster, reducing the number of patient visits and treatment time, improving symptoms sooner, and improving patient compliance. Studies have shown that using standardized antigens for RIT is safe and effective after drug pretreatment.[162-167] Patients in most areas of China are allergic to mites. Since 2012, Chinese researchers have conducted clinical studies on the safety and effectiveness of RIT in treating AR using standardized mite antigens. Furthermore, some studies have been conducted to examine the mechanism of RIT and how to conduct drug preconditioning.[168-170] Presently, nearly 10 hospitals in China have performed clinical trials using RIT (**Table 4**). However, due to the high risk of RIT, a multi-center study with a large sample size is needed to validate it for general application. Therefore, as RIT is not routinely recommended in China, caution should be taken in its application.

Dose adjustments

Dosage can be modified to make up for missed injections, and different adjustment rules apply to the build-up (**Table 5**) and maintenance phases (**Table 6**).

Table 4. Rush immunotherapy schedule

Build-up phase	No. of injection sequence	No. of injection bottle	Target volume (mL)	Target dose (SQ, U)	Time of injections
Day 1	1	1	0.1	10	08:30
	2	2	0.1	100	10:30
	3	3	0.1	1,000	14:30
Day 2	4	3	0.2	2,000	08:30
	5	3	0.4	4,000	10:30
	6	3	0.6	6,000	14:30
Day 3	7	3	0.8	8,000	08:30
	8	4	0.1	10,000	10:30
	9	4	0.2	20,000	14:30
Day 4	10	4	0.3	30,000	08:30
	11	4	0.4	40,000	14:30
Day 5	12	4	0.5	50,000	08:30
	13	4	0.5	50,000	14:30
Day 6	14	4	1.0	100,000	08:30

SQ, standard quality.

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Table 5. Dose adjustment rules in the build-up phase

Time interval since missed injection	Dose adjustment
Up to 7 days*	Continue as scheduled
8–13 days after missed scheduled injection	Repeat previous dose†
14–21 days after missed scheduled injection	Reduce dose 25%†
Over 21 days after missed scheduled injection	Reduce previous dose 50%†

*If on a weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection; †Then increase dose at each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

Table 6. Dose adjustment rules in the maintenance phase

Time interval since missed injection	Dose adjustment
Within 2 wk	Continue as scheduled
2–4 wk after missed scheduled injection	Return to 50% of last dose
4–8 wk after missed scheduled injection	Return to the lowest dose of the concentration of former level
8–12 wk after missed scheduled injection	Return to the lowest dose of the concentration of former 2 levels
Over 12 wk after missed scheduled injection	Restart from the initial concentration

It is suggested that if the diameter of the local urticaria exceeds 5 mm within 24 hours after injection, the dose should not be increased. Initiating AIT should be avoided during seasons of peak allergen exposure. The first dose should not exceed 50% of the last dose because each injection is in a new package. In cases of vaccine change, the immunotherapy procedure should be adjusted. According to Chinese government policy (National Health Commission of the People's Republic of China), there are no restriction intervals between inactivated vaccines and all oral vaccines; however, there should not be fewer than 28 days between injection doses of live vaccines. Approximately 90%–95% of recipients of a single dose of live vaccine administered by injection developed protective antibodies within 14 days of the dose, indicating that the optimal space between 2 vaccines is more than 14 days.[171] During the build-up phase, the patient can receive other vaccines, including the COVID-19 vaccine, 1 week after the allergen injection, followed by the regular allergen vaccine (second allergen injection). Additionally, the dose should be half of the last allergen vaccine dose. During the maintenance phase, the patient can receive other vaccines 1 week after the allergen injection, and 3 weeks later the patient can continue the immunotherapy schedule.

MANAGEMENT OF PATIENTS

AR patients

In the management of AR patients, SCIT in combination with pharmacotherapy, physical therapy, and allergen avoidance can improve the clinical efficacy and safety of the treatment. Therapy before, during, and after immunotherapy should be administered according to patient-specific requirements.[172]

Glucocorticoid nasal spray is the first-line treatment for AR. Oral or topical antihistamines can relieve nasal itching, sneezing, and runny nose. Furthermore, the combination of glucocorticoid and antihistamine nasal spray is more effective than a single drug. Avoidance of airborne pollutants, such as cigarette smoke, is also important for controlling AR.[173]

Management before SCIT

Before commencing SCIT, treatment should be given to patients to alleviate symptoms. Anti-allergy drugs, such as oral or topical H1-antihistamines and/or glucocorticoid nasal spray, are useful for treating AR-associated symptoms. In cases of nasal obstruction, a vasoconstrictor

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can be used for a short period of time, generally not more than 7 days. Additionally, nasal cavity irrigation is useful for easing nasal symptoms. These treatments can effectively control the symptoms and lay a foundation for SCIT.

Management during SCIT

During treatment, antihistamine premedication can significantly improve the safety and efficacy of SCIT by reducing the frequency and severity of AR and increasing the target maintenance dose.[174] Allergic symptoms may recur during SCIT when patients are exposed to high concentrations of allergens. In addition to SCIT, allergy medications, including glucocorticoid nasal spray and oral/topical antihistamines, can administered for more effective treatment.

Additionally, patients are advised to maintain a clean environment and rinse the nasal passages to reduce the presence of allergens in the air and nasal passages, respectively.[175]

Management after SCIT

Although SCIT has a long-term effect after completion, relapse may occur in some patients. Appropriate drugs can be administered to alleviate symptoms and consolidate the therapeutic effect.

AR with asthma

Historically, since AR and asthma exhibit common physiological and immune inflammatory mechanisms, they were considered different manifestations of the same allergic airway disease in the upper and lower airways, which means "one airway—one disease."[176,177] Moreover, AR is one of the risk factors for asthma, and the worldwide prevalence of AR is reported to be over 85% in patients with asthma.[178] In China, approximately 70% of asthmatic patients have AR, whereas only 10% of patients with AR have asthma.[20,179]

Management of patients with both AR and asthma is similar to that of asthmatic patients. AIT may be an option for these patients to effectively manage multiple symptoms. Moreover, in compliance with the review for personalized asthma care, Global Initiative for Asthma (GINA) 2021, which includes asthma diagnosis and assessment, and treatment and adjustment, is needed.[180] Studies have shown that AIT can ameliorate symptoms in patients, reduce medication requirements, and reduce the incidence of asthma and AR.[181-183]

Long-term treatments of asthma include controller medications, reliever medications, and add-on therapies for severe patients. For adults and adolescents, an inhaled corticosteroid (ICS)-containing controller treatment, which is a personalized asthma management, should be received as soon as asthma is diagnosed. In mild asthma, treatment with low-dose ICS-formoterol could be an effective alternative to relieve symptoms and reduce the risk of exacerbation. The response and possible side effects of asthmatic patients to treatments should be monitored and routinely reviewed to adjust treatment to any variable conditions. Controller medication can be adjusted in a stepwise manner during the AIT process for effective treatment and symptom management as stated in the GINA.[184]

Children

The treatment of patients with allergic diseases involves 2 aspects: in-hospital management and out-of-hospital management, which is achieved through patient, family, and caregiver education (including follow-up education).[185] In-hospital management involves electronic

and hardcopy (paper) medical databases, whereas out-of-hospital management mainly includes patient education, telephone reminders, and patient follow-up.[186]

Additionally, it is necessary to inform patients of the advantages and disadvantages of the treatment chosen, duration of treatment, possible adverse reactions and the risk of severe allergic reactions, costs, therapy efficacy, and long-term benefits.[187] In addition to telephone follow-up, communication via internet could be employed to establish close communications between physicians and patients, which can improve treatment efficiency and facilitate the recovery process.[130,188] China Children's Asthma Action Plan (CCAAP) is a scientific, practical, and professional electronic management platform for improving the care and management of children with asthma. A similar management approach could be applied to SCIT in children.

EFFICACY

Subjective evaluation

Based on the Chinese guidelines for the immunotherapy of AR, it is recommended that AIT be initiated earlier for effective treatment outcomes.[158] Once AR is diagnosed and the relevant causal allergen identified, AIT should be considered the initial treatment option.[149] Clinical studies have shown that 85.4% of patients were responsive to SCIT therapy after 3 years of SCIT.[189]

SCIT can relieve nasal mucosal inflammation in AR patients, reducing mucosal pallor and edema, and significantly improve nasal symptoms including congestion, discharge, itching, and sneezing.[189,190] SCIT can significantly reduce the need for allergy medications as well as improve the quality of life and mental health status of AR patients.[148,191] SCIT can attenuate both the upper and lower airway immune responses to nasal allergen exposure in patients with AR and/or asthma.[192] Patients with AR and asthma were treated with SCIT for 3 years and followed-up for 2 years; the results indicated that SCIT had a long-term effect in reducing the risk of asthma development.[190] An analysis of SCIT in children with AR and cough variant asthma showed that SCIT not only significantly improved the clinical symptoms, but also prevented the development of new sensitization and typical asthma.[193] An analysis of SCIT efficacy showed that HDM-SCIT significantly improved nasal symptoms and quality of life in children and adults with AR, with longer effects in children than in adults.[189,194] For AR patients sensitized to multiple aeroallergens, SCIT treatment can also significantly improve clinical symptoms.[148]

Moreover, several studies have confirmed that SCIT exhibits long-term effects in AR patients.[115,148,195] A long-term follow-up study of AR patients who received 3 years of SCIT showed that clinical efficacy lasted for at least 5 years.[195] Sahin *et al.*[196] showed that the positive effects of SCIT were evident in patients 10 years after HDM-SCIT.

SCIT can be divided into conventional and cluster immunotherapy during the dose accumulation phase. Studies have found that cluster immunotherapy can significantly reduce nasal symptoms in AR patients, with rapid effects compared to conventional immunotherapy. Moreover, compared to the conventional immunotherapy regimen, the cluster regime did not significantly affect the incidence of local or systemic adverse reactions during the dose accumulation and dose maintenance phases.[197,198] Therefore, cluster immunotherapy could be a safe, rapid, effective treatment procedure for AR.

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Nasal allergen provocation test

NAPT is required to imitate the natural environment or conditions in order to determine specific allergens. Clinicians use sprays directly or place suspected causative antigens into the nasal cavity to observe which antigens trigger pathophysiological reactions for diagnosis. NAPT has been regarded as a safe and straightforward technique for the diagnosis of AR. NAPT is the internationally recognized "gold standard" for the diagnosis of AR and applied to identify the disease phenotype before commencing AIT in order to ascertain allergens. The results of NAPT include subjective assessments (VAS and total nasal symptom score) and objective assessments (peak nasal inspiratory flow, acoustic rhinometry, and active anterior rhinomanometry).[199]

Biological markers

Biomarkers play an important role in predicting the efficacy of AIT and monitoring the treatment response. There are 6 classes of potential biomarkers of AIT: antibodies (total IgE, sIgE, sIgE/IgE ratio, sIgG1, sIgG4, sIgE/IgG4 ratio, and sIgA); basophil activation (CD63, CD203c, and basophil histamine release); cytokines and chemokines (IL-4, IL-10, IL-13, IL-9, IL-17, and eotaxin); cellular markers (Tregs, Bregs, and DCs); serum inhibitory activity for IgE (IgE-FAB); and allergen provocation tests (SPTs, intradermal test, nasal provocation test, and environmental exposure chamber).[200]

Serum sIgE level is an inclusion criterion for the initiation of immunotherapy. Moreover, because of their high specificity and easy detectability, antibodies, especially sIgE, sIgG4, and the sIgE/IgG4 ratio, have been widely used to predict the efficacy of clinical immunotherapy and evaluate response. However, antibody levels are not always consistent with clinical outcomes.

Data regarding the clinical relevance of HDM components over AIT for AR are lacking. Huang *et al.*[201] examined the serum sIgE and sIgG4 level of 18 adult AR patients receiving HDM AIT for 52 weeks and found that Der p1, p2, p23, Der f1, and f2 were important sensitizing components of HDM. Der p1 appears to be the most clinically relevant allergenic component for effective AIT.

Basophil activation is measured by flow cytometry using the dose-response curves after allergen stimulation *in vivo*. Surface markers used in basophil activation tests include CD63, CD203c, and diamine oxidase. Most studies use CD63 as an activation marker, whereas CD203c is basophil-specific. The basophil activation test has been used to monitor the effects of AIT and other immune modulatory therapies.[202] Decrease in basophil activation after SCIT was reported in patients with allergic rhinoconjunctivitis caused by grass pollen.[203]

Weihong *et al.*[204] evaluated serum cytokines in 72 pediatric AR patients receiving SCIT. Multiple cytokine profiling was conducted via Luminex assay at baseline, and 48 selected cytokines were tested and compared between the defined effective (n = 46) and ineffective group (n = 23). The serum eotaxin, interferon (IFN)-γ, IL-4, and MIF levels were closely associated with the efficacy of SCIT in HDM-induced pediatric AR patients. Further, enzyme-linked immunosorbent assay validation results in a cohort of 80 pediatric patients demonstrated that serum eotaxin and IL-4 levels were increased in responders, whereas IFN-γ levels decreased significantly ($P < 0.05$ for all); ROC curves revealed that serum IL-4 exhibited more reliable accuracy in predicting SCIT efficacy than eotaxin and IFN-γ.

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IgE-FAB measures the serum inhibitory activity for IgE after AIT by flow cytometry. Some data support the role of IgE-FAB in predicting the efficacy of AIT. The IgE-FAB assay technique is complex and can only be performed in specialized laboratories, limiting its clinical application.[205]

Apart from *in vitro* examination, *in vivo* biomarkers, including various allergen provocation tests, have been used to evaluate the curative efficacy of AIT. In addition to the biomarkers mentioned above, Ma *et al.*[206] recently reported that serum leukotriene A4 hydrolase (LTA4H) increased significantly after 1-year SCIT, which could be used as a new biomarker for AIT.

Efficacy in adults

Long-term efficacy in adults

SCIT has a definite long-term effect in most clinical trials, which has been stated in some international guidelines of immunotherapy for AR.[175] Durham *et al.*[207] found that there was a sustained decrease in mean rhinoconjunctivitis symptom and medication scores, and significant improvement in the quality of life in the active treatment group compared to the control group 1 year after 3 years of standard allergy immunotherapy. Peng *et al.*[190] reported, for the first time, that a 3-year SCIT course reduced the risk of developing asthma and treated clinical symptoms. Hence, it can be concluded that SCIT is not only a first-line treatment for AR but also a preventive treatment for other allergic airway diseases. A retrospective study[208] involving 8,396 monosensitized patients with allergic symptoms indicated that specific immunotherapy can reduce new sensitizations in AR patients. Furthermore, there was a decrease in allergies in the offspring whose parents had received AIT compared with those whose parents that did not undergo AIT.[209] Therefore, it is concluded that AIT may have a long-term effect, which transmits to offspring.

Short-term efficacy in adults

Presently, there are no precise objective indicators to evaluate the clinical efficacy of SCIT for AR. Generally, the efficacy of SCIT is assessed based on improvement in symptom and medication scores; however, the course points observed are usually different. Zhang *et al.*[155] reported significant improvements in the symptom, VAS, and medication scores of patients at the 6th week of cluster immunization, in contrast to 14th week of conventional immunization.

Feng *et al.*[39] found a significant improvement in symptom medication scores after 12 weeks of treatment during the up-dosing phase compared with the baseline; additionally, patients in the SCIT group had significantly lower scores than those in the medication group at 52–156 weeks during the maintenance phase.

Shin *et al.*[210] examined the efficacy of SCIT in 267 patients who had received immunotherapy for at least 1 year and found that approximately 13.3% of patients reported improvements in symptoms after 3 months of immunotherapy, 35.7% at 6 months, 72.6% at 12 months, and 92.1% at 24 months. Liu *et al.*[211] examined 83 patients who had completed 24 months of SCIT, and the effective rates, which is a decrease of more than 25% in the sum of symptom and medication scores, at 4, 6, 12, 18, and 24 months were 60.2%, 61.4%, 60.2%, 63.9%, and 67.4%, respectively.

Uriarte and Sastre[212] evaluated the efficacy of SCIT (3-week up-dosing phase and 12-month maintenance phase) in patients with cat or dog allergies and observed significant

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improvements in rhinitis and asthma symptoms, medication scores, VAS scores, and QoL questionnaires at 6 and12 months. Similarly, there were considerable improvements in symptoms 1 month after ultra-rush up-dosing phase and 6 months of maintenance phase.[213]

Kepil *et al.*[214] reported significant decrease in VAS and medication scores and significant improvement in rhninoconjunctivetis quality-of-life questionnaire score in patients with pollen allergy after 7-week SCIT, starting 3 months before the allergy season, compared with baseline values and those of patients in the placebo group. Some Chinese researchers evaluated the efficacy of SCIT in patients with *Artemisia* pollen allergy and found the 1-year effective rate was 66.7%–76.4%.[206,215]

Efficacy in children

In China, SCIT has been widely used for the treatment of allergic diseases in children since the 1990s. Over the past 20 years, several national academies and guidelines have recommended the integration of SCIT into the standard treatment for AR.[129,185,216]

According to current guidelines based on the latest evidence, allergen-specific immunotherapy should be administered to children with moderate to severe AR, and the recommended starting age is 5 years old.[217,218] Several studies have confirmed the reliable therapeutic effect of AIT in children with AR.[148,219] For instance, a study reported a considerable decrease in symptom scores after 4 months of allergen-specific immunotherapy, and these continued to decline during a period of 12-month SCIT.[220] Wang *et al.*[217] found that the level of serum sIgG4 increased significantly after 1-year SCIT treatment. These results are consistent with the previous findings of Zhang *et al.*[155,220] who observed considerable improvements in symptoms within the first year of specific subcutaneous injection treatment; however, patients were prone to recurrence of symptoms. Wang *et al.*[217,221] reported that improvement in symptoms remained stable in the second and third years of SCIT. Several clinical investigations revealed that 2–3 years of SCIT is more effective than traditional medical treatment for treating clinical symptoms and improving the quality of life of children with AR, and that the clinical benefits persist for more than 5–10 years after treatment cessation.[222,223] SCIT has an ideal long-term protective effect in children with AR; however, it takes at least 2–3 years of treatment for a sustained therapeutic effect. Song *et al.*[148] found that single-allergen SCIT is beneficial for treating AR caused by multiple allergens in pediatric populations. Furthermore, Penagos *et al.*[222] showed that SCIT had better effects in children with AR than in adults with AR. The optimal time for SCIT is during childhood because the immune systems of children are not fully matured.

AIT is the only etiological treatment for AR, it involves regulating the natural process of AR through immune regulation mechanisms.[224] HDM is the most common allergen responsible for AR in China.[224] Because of the existence of cross antigen mechanisms, the number of allergens, including HDMs, is 2–3, which is also the indication of single HDM SCIT. SCIT can significantly improve the symptoms and quality of life of children with AR during a long period of time, and it is significantly better than conservative treatment. SCIT does not only have an early curative effect, but also a long-term curative effect. Studies have shown that 3-year SCIT can significantly improve HDM respiratory allergic reactions and 5-year SCIT can improve clinical symptoms of AR.[181] Moreover, there was a decrease in the incidence of new allergic reactions during treatment and several years after the completion of SCIT,[225] with a significantly reduced risk of asthma.[133] Furthermore, some research reports suggest that the impact of SCIT in children is better than that in adults.[189]

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SAFETY OF IMMUNOTHERAPY

Adverse reactions

Local reactions (LRs)

LRs from SCIT commonly occur. The frequency of LRs range from 26% to 86%, and most LRs occur during the dose-accumulation phase.[226] Zhang *et al.*[227] reported the LR rate of 3.0% per injection and 34.7% per patient in China. LRs are defined as pruritus, redness, pain associated with swelling, and erythema/subcutaneous nodules that occur at or near the injection site.[226-228] LRs are divided into immediate or delayed reactions depending on the time when they occur.[228] According to the size of the patient's palm, LRs are classified into small and large LRs.[228] LRs are not associated with subsequent SRs, which means that it does not predict future SRs. Additionally, dose adjustment after LRs is mostly unnecessary.

LRs are results of both IgE and non-IgE cutaneous responses.[228] Irritant and hygroscopic are other mechanisms,[229,230] and higher body mass index and HDM sIgE level in children are risk factors for LRs.[231] Studies have shown that pretreating nonsteroidal anti-inflammatory drugs or antihistamines, using depot immunotherapy with aluminum hydroxide, applying cold compress at the injection site, alternating injection sites or splitting the dose into 2 injections in each arm, adding an epinephrine rinse, and using a dry needle to inject the allergen can reduce the incidence of LRs.[226]

SRs

SCIT is a safe well-tolerated treatment if injections are given in a medical setting by experienced physicians.

Previous studies suggest that the incidence rate of SRs in AR patients range from 1.3% to 14%.[132,232-235] The incidence rate of SRs per injection with conventional nonaccelerated build-up protocols is about 0.1%–0.2%,[233,236] although it is higher if accelerated cluster or rush build-up regimens are used.[237,238] The incidence of fatal severe reactions was reported as 1 event per 1–2.5 million injections[233,238,239] in the past, whereas new data collected in the North American Surveillance Study between 2008 and 2019 showed a decrease in incidence to 1 in every 7.2 million injections.[240] As expected, most SRs (75.8%) occurred during the up-dosing phase.[139]

SRs to SCIT can range from mild to severe adverse reactions in the skin, gastrointestinal tract, upper and lower airways, or the cardiovascular system. Several classifications of SRs during AIT have been proposed, including the EAACI 2006 Grading System[241] (EAACI2006), WAO 2010 Grading System[236] (WAO2010), WAO 2017 Grading System[232] (WAO2017), and AAAAI/ACAAI Grading System.[242] The detailed grading systems are shown in **Table 7**.[243]

Although different grading systems and severities are closely related, there are variations in the grading of mild and moderate SRs. Both the AAAAI/ACAAI classification and the EAACI2006 classification are easily administered and reliable. The main limitations in the EAACI2006 classification are the lack of gastrointestinal symptoms, the rigid definition of "early onset" as 15 minutes, and the lack of precision of some terms. The WAO2010 classification was based on the organ system(s) involved and reaction severity. The final grade is determined by the physician/health care professional after the event is over. The WAO2010 classification system is considered more practical and convenient for diagnosis and helpful in accurately deciding when epinephrine should be used. The WAO2017 classification has not been endorsed by the WAO, and the correlation between the grade and

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Table 7. The different international grading systems (EAACI2006, WAO2010, and AAAAI/ACCAI)

Grading system	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
EAACI2006	Regardless of the severity, any of the following nonspecific symptoms: decreased blood pressure (sensation), sensation of foreign body, fatigue, headache, nausea, vomiting, dizziness, and tachycardia	Regardless of severity if any of the following: abdominal pain, chest discomfort, chest tightness, diarrhea, dysphagia; or, if any of the following and mild severity: asthma, bronchospasm, cough, dysphonia, dyspnea, erythema, rhinitis, urticaria, wheezing, and conjunctivitis	Any of these symptoms when severity is moderate and onset is 15 min or later: asthma, bronchospasm, dyspnea, generalized erythema, generalized pruritus, rhinitis, urticaria, wheezing, conjunctivitis, and laryngeal edema	Any of these symptoms when intensity is moderate and the onset is earlier than 15 min: generalized erythema, generalized pruritus, urticaria, angioedema/laryngeal edema and wheezing; or any of the following regardless of the onset if intensity is severe: asthma, angioedema, bronchospasm, dyspnea, generalized erythema, generalized pruritus, urticaria, flushing, and wheezing	When hypotension or loss of consciousness is present	NA
WAO2010 AIT	NA	Only a single organ affected with any of these symptoms in mild reaction: angioedema, erythema, generalized erythema, pruritus generalized, urticaria, flushing, cough, dysphonia, rhinitis, dizziness, syncope, headache, blood pressure decrease (subjective feeling), fatigue, sensation of foreign body, nausea, dysphagia, and tachycardia	When 2 organs are affected with mild severity; or, if any of the following alone with mild severity: asthma, bronchospasm, chest discomfort, chest tightness, wheezing, dyspnea, vomiting, abdominal pain, and diarrhea	If any of the following along with moderate severity: asthma, bronchospasm, chest discomfort, chest tightness, dyspnea, and wheezing; or, if laryngeal edema with mild severity	If any of the following along with severe affection: asthma, bronchospasm, chest discomfort, chest tightness, dyspnea, and wheezing; or if any of the following regardless of severity: hypotension or loss of consciousness	Death
AAAAI/ACAAI	NA	If mild severity, 1 or more of the following: generalized erythema, generalized pruritus, flushing, rhinitis, conjunctivitis, erythema, generalized erythema, urticaria, chest discomfort, chest tightness, angioedema, and laryngeal edema	If any of the following with mild or moderate severity: asthma, bronchospasm, dyspnea, wheezing; or, when moderate severity if any of the following: rhinitis, cough, dysphonia, urticaria, abdominal pain, diarrhea, dysphagia, nausea, vomiting, chest discomfort, and chest tightness	If any of the following along with severe presentation of: asthma, bronchospasm, dyspnea, and wheezing; or, any of the following regardless of the severity of the reaction: hypotension, loss of consciousness	NA	NA

NA, not applicable.

SR severity is lower in this classification system compared with the WAO2010. Although these classification systems have been used in several clinical reports and reviews, they are yet to be clinically validated.[243]

Delayed reactions are defined as SRs occurring more than 30 minutes after injections. Skin disorders, particularly urticaria, were more frequently observed after 60 minutes. Incidences of delayed reactions have been estimated to be 14%–15% of all SRs,[233] with only 0.5% of SRs occurring after 60 minutes. Most of these delayed SRs were rated as mild or moderate, were rarely fatal. For patients with delayed SR, it would be advisable to increase their wait time to 45–60 minutes or longer. Because of poor adherence with epinephrine self-administration, prescribing autoinjectors for all patients is highly controversial. Thus, it is not an effective alternative to observing patients for at least 30 minutes following SCIT injections.[233]

Before discharge, patients should be counseled on the possibility of biphasic reactions. Biphasic reactions from occur in 10%–23% of patients, at a median time of 5.5 hours, and are typically milder.[244,245]

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Risk factors

AIT is contraindicated in patients with medical conditions that might increase the risk of treatment-related severe SRs, such as those with severe or poorly controlled asthma or with significant cardiovascular disease (*e.g.*, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension). Therefore, AIT should be administered with caution to patients receiving β-blockers or angiotensin-converting enzyme inhibitors. Risk factors for SCIT-related SRs include symptomatic asthma, prior SCIT-related SRs, and higher degree of skin test reactivity.[139] Other potential risk factors for SCIT-related SRs, such as administration during the height of the pollen season, build-up dosing schedule (cluster *vs.* conventional), and treatment phase (maintenance vs. build-up phase) have been suggested, but none have been clearly established.[238] Dong *et al.*[246] reported that SRs during immunotherapy are high in young asthmatic patients with high degree of allergen sensitivity. Some risk factors for severe AEs and fatal events are shown in **Table 8**.[244,247-250]

Safety in children

Among Chinese children, SCIT-related adverse reactions occurred at a rate of 38.4% per patient and 10.0% per injection during SCIT for AR and bronchial asthma.[251] LRs accounted for 88.9% of the adverse reactions, and occurred at a rate of 35.6% per patient and 8.9% per injection during SCIT, with intense LRs observed in only 2.8% of patients (wheal diameter > 8 cm).[251] Additionally, the majority (80.2%) of LRs occurred within 60 minutes of injection.[231] SRs accounted for a minority (11.1%) of the adverse reactions,[251] and occurred at a rate of 0.5%–2.60% per injection and 9.2%–19.3% per patient during SCIT.[227,231,246,251-253] Some patients experienced SRs 2 times or more.[231,253] According to the World Allergy Organization SCIT SR grading system, all the SRs reported ranged from grades 1 to 3, and no grades 4 or 5 SRs were reported.[227,231,252,253] Additionally, no fatal cases were reported.[148,251] Most SRs occurred during injection of No.4 vial (AlutardDp vaccine),[231,253] and approximately 89.3%–95.8% occurred within 30 minutes of injection.[227,246,253] Treatment with medications, such as β_2 agonists and H1 antihistamines, was generally effective against SRs; however, intramuscular injection of epinephrine was occasionally necessary.[231,246,251,253] The prevalence of SRs was higher in children 5–11 years old than in children 12–17 years old.[253] SCIT has a safe profile in children with allergic diseases.[254]

Table 8. Conditions potentially associated with subcutaneous immunotherapy-related systemic reactions

Risk factors
Lower age
Administration-related factors
Missed dose adjustment during pollen peak
Allergen composition and mixtures
Accelerated build-up regimens
Short time of observation after injection
Needle length ≥ 13 mm
Delayed epinephrine administration
Dosing errors
Non-specific patient-related factors
With asthma
Uncontrolled asthma (contraindication)
Long-term therapy with non-cardioselective b-blockers and ACE inhibitors
Specific patient-related factors
Previous systemic and local reactions
High degree of allergen sensitivity

ACE, angiotensin converting enzyme.

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Safety comparison of different schedules

Studies have shown that there was no significant difference in the incidence of systemic AEs between cluster and conventional SCIT. During the maintenance phase, similar improvements in quality of life and reduced skin reactivity were observed in both groups, but no significant changes in sIgE were observed.[155] There was no significant difference in the incidence of LRs or SRs during the build-up and maintenance phases between the cluster and conventional schedules.[197,255,256] Conventional and cluster SCIT are important immune-modifying treatment schedules for both children and adult AR patients, with similar efficacies in both adults and children.[257] The cluster schedule is as safe as the conventional schedule for AR patients with or without asthma.[156]

Conventional immunotherapy is effective in treating AR; however, the treatment strategy is limited by poor patient compliance, delayed efficacy, and patient frustration. RIT is a technique for treating allergic patients using a series of injections of allergenic extracts until an immunizing (maintenance) dose is attained within a short period of time.[258-260] RIT offers the advantages of rapid response, improved compliance, and cost-effectiveness, and can shorten treatment duration from 4 months in conventional schedules to less than 1 week.[254] However, considering the high risk of serious adverse reactions compared to the conventional immunotherapy,[261-263] its use is limited in China. There are few studies on RIT for AR.[254] Most published RIT studies have focused on allergic patients with venom. Most venom RIT studies have demonstrated that the efficacy and safety of venom RIT are equivalent to or better than those of conventional schedules.[261]

Studies on RIT in AR patients with or without asthma suggest that RIT without premedication can increase the risk of SRs, with SR rates of 27%–100% for patients without premedication and 7.2%–27% for patients with premedication. Premedication appears to reduce the SR rate to a range that is comparable to conventional build-up schedules, which is 0.84%–28.6%.[261] Qiu *et al.*[169] compared the safety and efficacy of RIT and conventional immunotherapy in Chinese AR patients. For safety, all RIT patients were hospitalized for 6 days and received oral antihistamines and corticosteroids during RIT. Results showed that the LR rates of the RIT and conventional immunotherapy groups during the build-up phase were 32.45% and 30.86%, respectively. In contrast, SRs were observed in 12.2% and 12.5% of all patients in the RIT and conventional immunotherapy groups, respectively. Therefore, it can be concluded that the safety and efficacy of RIT in premedicate AR patients is similar to those in patients undergoing conventional immunotherapy.

Although there have been several reports on the safety of RIT and a decrease in the incidence of allergic reactions, especially systemic allergic reactions after premedication, there is a lack of large-scale research reports on patients in China. Therefore, allergists should be careful in patient selection for this procedure because anaphylaxis can occur. Due to careful patient selection, routine premedication, and lower targeted end-point dosage, the risk of SRs has reduced considerably[264]; however, RIT should be performed in medical institutions under the supervision of experienced professionals to ensure safe and effective immunotherapy for AR.[254,261,264,265]

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MANAGEMENT OF ADVERSE REACTIONS

Prevention

Factors that contribute to adverse reactions during AIT include patient-related factors (sex, age, asthma, and high sensitivity constitution), antigenic vaccine factors (antigenic component and administration route), and dose-related factors of antigen vaccines (administration mode, history of allergic attack), *etc*.

Based on the above risk factors, the following considerations should be noted to prevent serious adverse reactions caused by AIT:

- Before starting immunotherapy, patient health education should be performed on the possible causes and triggers of adverse reactions.[49]
- Patient health status, including drug usage, asthma treatment, and pulmonary function, should be assessed before each injection.[254]
- Patients should be allowed to rest for more than 15 minutes before injection. Additionally, precautionary treatments, such as oral antihistamine or anti-IgE drugs, should be taken 30 minutes–1 hour in advance.
- Ensure that emergency medicines and equipment are available and ready.
- Ensure that the injection dose is correct.
- Reduce the dose of immunotherapy as appropriate in the pollen spreading season.[266]
- Ensure that observation time after injection is not less than 30 minutes; this can be extended to 1–2 hours if necessary.[246]
- In cases of SRs, ensure the AIT injection dose is reduced or treatment is terminated.[169]

Treatment of adverse reactions

Generally, most patients are tolerant to AIT, but a few adverse reactions require appropriate treatment. The rules and procedures for managing local and systemic adverse reactions are outlined below.

Mild LRs, such as redness, irritation, or swelling at the site of injection, can usually be relieved using topical corticosteroids, ice packs, or oral antihistamines.[267] However, patients with mild adverse reactions should be observed closely and any worsening symptoms should be evaluated carefully as potential signs of anaphylaxis.

Due to the risk of anaphylaxis, more attention should be paid to LRs and SRs, especially for SCIT.[268,269] Early signs should be identified including itching of the palms and soles, perianal or peri-genital pruritus, bellyache, urge to defecate and urinate, sneezing attacks, and generalized pruritus. Subsequently, respiratory and/or cardiovascular symptoms may appear.[265] The management of severe local and systemic adverse reactions in SCIT is summarized in **Table 9**.[241,270-272]

Since adverse reactions usually occur within 30 minutes after injection, patients must be observed for at least 30 minutes following injection. Additionally, injections must be administered by experienced clinicians in a standard hospital well equipped with emergency facilities including the following apparatuses: trolleys for patient to lie flat if needed; electrocardiographs, pulse oximeters and blood pressure monitors; oxygen and suction devices, including tubing and masks; airway management devices for intubation and cricothyrotomy; intravenous infusion pumps; nebulizer masks (for inhaled epinephrine); manual blood pressure cuffs; intravenous access cannulae (20–16 G) and giving sets; and needles and syringes.[272]

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Table 9. Management of adverse reactions in subcutaneous immunotherapy

Grade	Description of adverse reactions	Management
Severe local adverse reactions	Wheals of diameter > 4 cm (redness, itching, pseudopods)	(I) Tie a tourniquet around the proximal allergen injection side (II) Give epinephrine 1:1,000 at a dose of 0.1–0.2 mL I.M. around the allergen injection site (maximum 0.5 mg) (III) Steroid cream should be applied at the local site (IV) Antihistamine oral or I.M. if necessary
Mild and moderate systemic adverse reactions	Wheals of diameter > 4 cm (redness, itch, and pseudopods), accompanied with one or more organs involved, including cutaneous (generalized pruritus, urticaria, flushing, subcutaneous angioedema, etc.); or upper respiratory and lower respiratory (rhinitis and asthma); or conjunctivitis or gastrointestinal (abdominal cramps, vomiting, or diarrhea)	(I) The first three rules are the same as rules 1, 2, and 3 for the management of severe local adverse reactions (II) Antihistamine eye drops for conjunctivitis (III) Antihistamine I.M., for example, diphenhydramine hydrochloride 40 mg I.M. (IV) Inhaled short-acting beta-2 agonists should additionally be given to relieve symptoms of bronchoconstriction (V) Establish the venous access (VI) Steroid I.V., e.g., methylprednisolone 40–80 mg (VII) Monitor blood pressure and pulse
Severe systemic adverse reactions	Early signs should be identified: palms and soles itch, perianal or peri-genital pruritus; an urge to defecate and urinate; sneezing attacks; and generalized pruritus. Also, respiratory and/or cardiovascular symptoms may follow	(I) Epinephrine 1:1,000 at a dose of 0.3 mL I.M. for patients weighing > 30 kg (II) The next five rules are the same as for rules 3, 4, 5, 6, and 7 for the management of mild and moderate systemic adverse reactions (III) Oxygen administration (IV) Other symptomatic treatments

I.M., intramuscular; I.V., intravenous.

As recommended in the guidelines, it is essential to carefully examine patients and their medical histories before administration of each injection. PEF evaluation must be performed before each injection, especially for AR patients with asthma. PEF values of less than 70% of the best predicted is considered a warning signal.[272] Most of the severe systemic AEs can be prevented if physicians abide by these rules.

In comparison to SCIT, SLIT has a less worrisome safety profile, as SRs are rare. Although no SLIT-associated severe systemic adverse reactions have been reported in China, patients should be educated on the possible adverse reactions they might experience during the procedure.

COVID-19 AND IMMUNOTHERAPY

In the face of the COVID-19 pandemic, the allergy communities all over the world have responded by mobilizing practice adjustments and embracing new paradigms in the care of AR patients to protect both patients and staff from SARS-CoV-2 exposure. In this review, some measures adopted in the management of AR in China during the COVID-19 pandemic, especially how to aid patients in continuing to receive AIT during the pandemic, are reported here for the first time.[273] During the off-peak period of the COVID-19 epidemic, patients could receive SCIT in the hospital as usual.[274] In most of the affected areas and during the epidemic peak outbreak, SCIT schedule modification or halting of treatment was recommended until the pandemic measures were lifted.[274] For dosage adjustment plans in cases of delayed treatment for SCIT in the build-up phase or maintenance phase, healthcare professionals should refer to the drug instructions.[254] A recent multicenter study examined the effect of SCIT delay (an interval of more than 2 weeks in the build-up phase and 6 weeks in maintenance phase) due to the COVID-19 pandemic in 643 AR patients and confirmed the long-term efficacy of SCIT for AR patients.[275] Most recently, Xi *et al.* published a novel dose adjustment SCIT schedule that began with a 10,000 SQ-U dosage and demonstrated that it was as effective and safe as the conventional schedule that started with a 10 SQ-U dosage for delayed SCIT of more than 16 weeks in the maintenance phase.[276] However, the correlation

between the mechanisms underlying SCIT and COVID-19 are still unclear and deserve further research. A survey in Beijing showed that patients continue taking their prescribed asthma medications during the ongoing pandemic,[277] which demonstrated that telehealth possesses tremendous potential for SCIT management during the COVID-19 pandemic and should be strengthened in the near future.

PERSPECTIVE

With the advent of novel approaches and improved schedules, more feasible medical solutions are available for precise management of AIT for AR patients. However, further studies are needed to determine the optimal formulation and approach selection, optimal treatment strategies for multi-sensitized patients and patients with underlying conditions, and reliable biomarkers for predicting responsiveness. Additionally, studies should examine the efficacy of the present treatment schedules (ordinary, cluster, and rush schedules) and possible modifications in the treatment of AR. Furthermore, novel and more efficient allergen vaccines should be developed.

The COVID-19 pandemic presents a considerable challenge for both patients undergoing and clinicians performing AIT. Long-term isolation or quarantine, and strict travel regulations limit hospital visits for AIT. To overcome this challenge, telehealth, which involves patients' education and allows consultation and treatment over the telephone and Internet, should be embraced. The development of highly efficient and safe administration routes and vaccines is desirable. Although the pandemic has presented a significant challenge in clinical practice, it has provided health care professionals and governments across the world the chance to reexamine and reassess the current AR management system and make necessary policies and technical changes.

Currently, the number of standardized allergen vaccines on the Chinese market is limited. Presently, there are only perennial indoor dust mite allergens and sublingual products for the most common outdoor allergen *Artemisia* pollen. In contrast, the number of AR patients is steadily increasing by approximately 100,000 each year, which is considerably more than the available treatment facilities and products. Therefore, to meet patient treatment needs, AIT should be vigorously promoted in China.

REFERENCES

1. Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, et al. Chinese Society of Allergy Guidelines for diagnosis and treatment of allergic rhinitis. Allergy Asthma Immunol Res 2018;10:300-53.
PUBMED | CROSSREF
2. Li X, Xu X, Li J, Huang Y, Wang C, Zhang Y, et al. Direct and indirect costs of allergic and non-allergic rhinitis to adults in Beijing, China. Clin Transl Allergy 2022;12:e12148.
PUBMED | CROSSREF
3. Wang XY, Ma TT, Wang XY, Zhuang Y, Wang XD, Ning HY, et al. Prevalence of pollen-induced allergic rhinitis with high pollen exposure in grasslands of northern China. Allergy 2018;73:1232-43.
PUBMED | CROSSREF
4. Ma T, Wang X, Zhuang Y, Shi H, Ning H, Lan T, et al. Prevalence and risk factors for allergic rhinitis in adults and children living in different grassland regions of Inner Mongolia. Allergy 2020;75:234-9.
PUBMED | CROSSREF

5. Tong H, Gao L, Deng Y, Kong Y, Xiang R, Tan L, et al. Prevalence of allergic rhinitis and associated risk factors in 6 to 12 years schoolchildren from Wuhan in Central China: a cross-sectional study. Am J Rhinol Allergy 2020;34:632-41.
PUBMED | CROSSREF
6. Zheng M, Wang X, Wang M, She W, Cheng L, Lu M, et al. Clinical characteristics of allergic rhinitis patients in 13 metropolitan cities of China. Allergy 2021;76:577-81.
PUBMED | CROSSREF
7. Guan K, Liu B, Wang M, Li Z, Chang C, Cui L, et al. Principles of allergen immunotherapy and its clinical application in China: contrasts and comparisons with the USA. Clin Rev Allergy Immunol 2019;57:128-43.
PUBMED | CROSSREF
8. Baldacci S, Maio S, Cerrai S, Sarno G, Baïz N, Simoni M, et al.; HEALS Study. Allergy and asthma: effects of the exposure to particulate matter and biological allergens. Respir Med 2015;109:1089-104.
PUBMED | CROSSREF
9. Deng SZ, Jalaludin BB, Antó JM, Hess JJ, Huang CR. Climate change, air pollution, and allergic respiratory diseases: a call to action for health professionals. Chin Med J (Engl) 2020;133:1552-60.
PUBMED | CROSSREF
10. Wang L, Qu F, Zhang Y, Weschler LB, Sundell J. Home environment in relation to allergic rhinitis among preschool children in Beijing, China: a cross-sectional study. Build Environ 2015;93:54-63.
CROSSREF
11. Teng B, Zhang X, Yi C, Zhang Y, Ye S, Wang Y, et al. The association between ambient air pollution and allergic rhinitis: further epidemiological evidence from Changchun, Northeastern China. Int J Environ Res Public Health 2017;14:E226.
PUBMED | CROSSREF
12. Chu H, Xin J, Yuan Q, Wang M, Cheng L, Zhang Z, et al. The effects of particulate matters on allergic rhinitis in Nanjing, China. Environ Sci Pollut Res Int 2019;26:11452-7.
PUBMED | CROSSREF
13. Ouyang Y, Xu Z, Fan E, Li Y, Miyake K, Xu X, et al. Changes in gene expression in chronic allergy mouse model exposed to natural environmental PM2.5-rich ambient air pollution. Sci Rep 2018;8:6326.
PUBMED | CROSSREF
14. Zhao R, Guo Z, Dong W, Deng C, Han Z, Liu J, et al. Effects of PM2.5 on mucus secretion and tissue remodeling in a rabbit model of chronic rhinosinusitis. Int Forum Allergy Rhinol 2018;8:1349-55.
PUBMED | CROSSREF
15. Sun N, Deng C, Zhao Q, Han Z, Guo Z, Wang H, et al. Ursolic acid alleviates mucus secretion and tissue remodeling in rat model of allergic rhinitis after PM2.5 exposure. Am J Rhinol Allergy 2021;35:272-9.
PUBMED | CROSSREF
16. Sun N, Niu Y, Zhang R, Huang Y, Wang J, Qiu W, et al. Ozone inhalation induces exacerbation of eosinophilic airway inflammation and Th2-skew immune response in a rat model of AR. Biomed Pharmacother 2021;137:111261.
PUBMED | CROSSREF
17. Ouyang Y, Yin Z, Li Y, Fan E, Zhang L. Associations among air pollutants, grass pollens, and daily number of grass pollen allergen-positive patients: a longitudinal study from 2012 to 2016. Int Forum Allergy Rhinol 2019;9:1297-303.
PUBMED | CROSSREF
18. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. Allergy 2015;70:245-56.
PUBMED | CROSSREF
19. Gruzieva O, Gehring U, Aalberse R, Agius R, Beelen R, Behrendt H, et al. Meta-analysis of air pollution exposure association with allergic sensitization in European birth cohorts. J Allergy Clin Immunol 2014;133:767-76.e7.
PUBMED | CROSSREF
20. Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet 2019;394:407-18.
PUBMED | CROSSREF
21. Zhang Y, Zhang L. Prevalence of allergic rhinitis in China. Allergy Asthma Immunol Res 2014;6:105-13.
PUBMED | CROSSREF
22. Chen ZG, Li YT, Wang WH, Tan KS, Zheng R, Yang LF, et al. Distribution and determinants of *Dermatophagoides* mites sensitization of allergic rhinitis and allergic asthma in China. Int Arch Allergy Immunol 2019;180:17-27.
PUBMED | CROSSREF

23. Lou H, Ma S, Zhao Y, Cao F, He F, Liu Z, et al. Sensitization patterns and minimum screening panels for aeroallergens in self-reported allergic rhinitis in China. Sci Rep 2017;7:9286.
PUBMED | CROSSREF

24. Li J, Sun B, Huang Y, Lin X, Zhao D, Tan G, et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. Allergy 2009;64:1083-92.
PUBMED | CROSSREF

25. Yang Y, Zhu R, Huang N, Li W, Zhang W, Wang Y, et al. The *Dermatophagoides pteronyssinus* molecular sensitization profile of allergic rhinitis patients in Central China. Am J Rhinol Allergy 2018;32:397-403.
PUBMED | CROSSREF

26. Wang W, Huang X, Chen Z, Zheng R, Chen Y, Zhang G, et al. Prevalence and trends of sensitisation to aeroallergens in patients with allergic rhinitis in Guangzhou, China: a 10-year retrospective study. BMJ Open 2016;6:e011085.
PUBMED | CROSSREF

27. Tang R, Sun JL, Yin J, Li Z. Artemisia allergy research in China. BioMed Res Int 2015;2015:179426.
PUBMED | CROSSREF

28. Chen IC, Lin YT, Hsu JH, Liu YC, Wu JR, Dai ZK. Nasal airflow measured by rhinomanometry correlates with FeNO in children with asthma. PLoS One 2016;11:e0165440.
PUBMED | CROSSREF

29. Kucuksezer UC, Ozdemir C, Cevhertas L, Ogulur I, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and allergen tolerance. Allergol Int 2020;69:549-60.
PUBMED | CROSSREF

30. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 2014;133:621-31.
PUBMED | CROSSREF

31. van de Veen W, Wirz OF, Globinska A, Akdis M. Novel mechanisms in immune tolerance to allergens during natural allergen exposure and allergen-specific immunotherapy. Curr Opin Immunol 2017;48:74-81.
PUBMED | CROSSREF

32. Shamji MH, Sharif H, Layhadi JA, Zhu R, Kishore U, Renz H. Diverse immune mechanisms of allergen immunotherapy for allergic rhinitis with and without asthma. J Allergy Clin Immunol 2022;149:791-801.
PUBMED | CROSSREF

33. Semitekolou M, Morianos I, Banos A, Konstantopoulos D, Adamou-Tzani M, Sparwasser T, et al. Dendritic cells conditioned by activin A-induced regulatory T cells exhibit enhanced tolerogenic properties and protect against experimental asthma. J Allergy Clin Immunol 2018;141:671-684.e7.
PUBMED | CROSSREF

34. Layhadi JA, Eguiluz-Gracia I, Shamji MH. Role of IL-35 in sublingual allergen immunotherapy. Curr Opin Allergy Clin Immunol 2019;19:12-7.
PUBMED | CROSSREF

35. Boonpiyathad T, Satitsuksanoa P, Akdis M, Akdis CA. Il-10 producing T and B cells in allergy. Semin Immunol 2019;44:101326.
PUBMED | CROSSREF

36. Yao Y, Wang ZC, Wang N, Zhou PC, Chen CL, Song J, et al. Allergen immunotherapy improves defective follicular regulatory T cells in patients with allergic rhinitis. J Allergy Clin Immunol 2019;144:118-28.
PUBMED | CROSSREF

37. Yao Y, Chen CL, Wang N, Wang ZC, Ma J, Zhu RF, et al. Correlation of allergen-specific T follicular helper cell counts with specific IgE levels and efficacy of allergen immunotherapy. J Allergy Clin Immunol 2018;142:321-324.e10.
PUBMED | CROSSREF

38. Sharif H, Acharya S, Dhondalay GK, Varricchi G, Krasner-Macleod S, Laisuan W, et al. Altered chromatin landscape in circulating T follicular helper and regulatory cells following grass pollen subcutaneous and sublingual immunotherapy. J Allergy Clin Immunol 2021;147:663-76.
PUBMED | CROSSREF

39. Feng M, Su Q, Lai X, Xian M, Shi X, Wurtzen PA, et al. Functional and immunoreactive levels of IgG4 correlate with clinical responses during the maintenance phase of house dust mite immunotherapy. J Immunol 2018;200:3897-904.
PUBMED | CROSSREF

40. Zhang H, Xian M, Shi X, Luo T, Su Q, Li J, et al. Blocking function of allergen-specific immunoglobulin G, F(ab')$_2$, and Fab antibodies prepared from patients undergoing *Dermatophagoides pteronyssinus* immunotherapy. Ann Allergy Asthma Immunol 2022;128:689-96.
PUBMED | CROSSREF

41. Tian GX, Peng KP, Liu MH, Tian DF, Xie HQ, Wang LW, et al. CD38$^+$ B cells affect immunotherapy for allergic rhinitis. J Allergy Clin Immunol 2022;149:1691-1701.e9.
PUBMED | CROSSREF

42. Liu X, Ng CL, Wang Y. The efficacy of sublingual immunotherapy for allergic diseases in Asia. Allergol Int 2018;67:309-19.
PUBMED | CROSSREF

43. Li TY, Chen DH, Lin ZB, Xu R. Efficacy of sublingual immunotherapy with dermatophagoides farinae drops in patients with allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;46:859-62.
PUBMED

44. Wang MS, Wu HT, Huang XB. Efficacy and economic evaluation of sublingual immunotherapy with Dermatophagoides farinae drops in patients with allergic rhinitis and allergic asthma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2016;30:538-42.
PUBMED

45. Lin Z, Liu Q, Li T, Chen D, Chen D, Xu R. The effects of house dust mite sublingual immunotherapy in patients with allergic rhinitis according to duration. Int Forum Allergy Rhinol 2016;6:82-7.
PUBMED | CROSSREF

46. Lin X, Lin H, Wei X, Huang Q. The efficacy and safety of sublingual immunotherapy in children and adult patients with allergic rhinitis. Allergol Immunopathol (Madr) 2017;45:457-62.
PUBMED | CROSSREF

47. Han L, You QJ, Li Z, Yang HH, Fang H, Zhang Y. Evaluation of efficacy of 1 year after completing the 2-year specific sublingual immunotherapy treatment course in allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2017;52:497-500.
PUBMED

48. Han M, Chen Y, Wang M. Sublingual immunotherapy for treating adult patients with allergic rhinitis induced by house dust mite among Chinese Han population: a retrospective study. Medicine (Baltimore) 2018;97:e11705.
PUBMED | CROSSREF

49. Li H, Chen S, Cheng L, Guo Y, Lai H, Li Y, et al. Chinese guideline on sublingual immunotherapy for allergic rhinitis and asthma. J Thorac Dis 2019;11:4936-50.
PUBMED | CROSSREF

50. Gao Y, Lin X, Ma J, Wei X, Wang Q, Wang M. Enhanced efficacy of dust mite sublingual immunotherapy in low-response allergic rhinitis patients after dose increment at 6 months: a prospective study. Int Arch Allergy Immunol 2020;181:311-9.
PUBMED | CROSSREF

51. Jin M, Zhang L, Zhou G, Zhang S, Li X, Hu S. The effect of the standard length of the first prescription on the adherence to sublingual immunotherapy for patients with allergic rhinitis. Int Forum Allergy Rhinol 2020;10:768-72.
PUBMED | CROSSREF

52. Lou H, Wang X, Wei Q, Zhao C, Xing Z, Zhang Q, et al. *Artemisia Annua* sublingual immunotherapy for seasonal allergic rhinitis: a multicenter, randomized trial. World Allergy Organ J 2020;13:100458.
PUBMED | CROSSREF

53. Yang J, Shen Z, Liu L, Kang W, Shao Y, Zhang P, et al. Clinical efficacy and safety of *Artesimia annua*-sublingual immunotherapy in seasonal allergic rhinitis patients based on different intervention time. Int Arch Allergy Immunol 2022;183:852-9.
PUBMED | CROSSREF

54. Hoang MP, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K. Intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Rhinology 2021;59:236-44.
PUBMED | CROSSREF

55. Wang K, Zheng R, Chen Y, Yu Q, Zhong H, Xiao P, et al. Clinical efficacy and safety of cervical intralymphatic immunotherapy for house dust mite allergic rhinitis: a pilot study. Am J Otolaryngol 2019;40:102280.
PUBMED | CROSSREF

56. von Moos S, Kündig TM, Senti G. Novel administration routes for allergen-specific immunotherapy: a review of intralymphatic and epicutaneous allergen-specific immunotherapy. Immunol Allergy Clin North Am 2011;31:391-406.
PUBMED | CROSSREF

57. Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A 2008;105:17908-12.
PUBMED | CROSSREF

58. Senti G, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. J Allergy Clin Immunol 2012;129:1290-6.
PUBMED | CROSSREF

59. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georén S, Winqvist O, et al. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. Respir Res 2016;17:10.
PUBMED | CROSSREF

60. Patterson AM, Bonny AE, Shiels WE 2nd, Erwin EA. Three-injection intralymphatic immunotherapy in adolescents and young adults with grass pollen rhinoconjunctivitis. Ann Allergy Asthma Immunol 2016;116:168-70.
PUBMED | CROSSREF

61. Lee SP, Choi SJ, Joe E, Lee SM, Lee MW, Shim JW, et al. A pilot study of intralymphatic immunotherapy for house dust mite, cat, and dog allergies. Allergy Asthma Immunol Res 2017;9:272-7.
PUBMED | CROSSREF

62. Hellkvist L, Hjalmarsson E, Kumlien Georén S, Karlsson A, Lundkvist K, Winqvist O, et al. Intralymphatic immunotherapy with 2 concomitant allergens, birch and grass: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2018;142:1338-1341.e9.
PUBMED | CROSSREF

63. Konradsen JR, Grundström J, Hellkvist L, Tran TA, Andersson N, Gafvelin G, et al. Intralymphatic immunotherapy in pollen-allergic young adults with rhinoconjunctivitis and mild asthma: a randomized trial. J Allergy Clin Immunol 2020;145:1005-1007.e7.
PUBMED | CROSSREF

64. Ahlbeck L, Ahlberg E, Björkander J, Aldén C, Papapavlou G, Palmberg L, et al. Intralymphatic immunotherapy with one or two allergens renders similar clinical response in patients with allergic rhinitis due to birch and grass pollen. Clin Exp Allergy 2022;52:747-59.
PUBMED | CROSSREF

65. Park HJ, Kim SH, Shin YS, Park CH, Cho ES, Choi SJ, et al. Intralymphatic immunotherapy with tyrosine-adsorbed allergens: a double-blind, placebo-controlled trial. Respir Res 2021;22:170.
PUBMED | CROSSREF

66. Skaarup SH, Schmid JM, Skjold T, Graumann O, Hoffmann HJ. Intralymphatic immunotherapy improves grass pollen allergic rhinoconjunctivitis: a 3-year randomized placebo-controlled trial. J Allergy Clin Immunol 2021;147:1011-9.
PUBMED | CROSSREF

67. Terada T, Omura S, Kikuoka Y, Suzuki M, Inaka Y, Inui T, et al. Sustained effects of intralymphatic pollen-specific immunotherapy on Japanese cedar pollinosis. Rhinology 2020;58:241-7.
PUBMED | CROSSREF

68. Thompson CP, Silvers S, Shapiro MA. Intralymphatic immunotherapy for mountain cedar pollinosis: a randomized, double-blind, placebo-controlled trial. Ann Allergy Asthma Immunol 2020;125:311-318.e2.
PUBMED | CROSSREF

69. Witten M, Malling HJ, Blom L, Poulsen BC, Poulsen LK. Is intralymphatic immunotherapy ready for clinical use in patients with grass pollen allergy? J Allergy Clin Immunol 2013;132:1248-1252.e5.
PUBMED | CROSSREF

70. Hellkvist L, Hjalmarsson E, Weinfeld D, Dahl Å, Karlsson A, Westman M, et al. High-dose pollen intralymphatic immunotherapy: Two RDBPC trials question the benefit of dose increase. Allergy 2022;77:883-96.
PUBMED | CROSSREF

71. Weinfeld D, Westin U, Hellkvist L, Mellqvist UH, Jacobsson I, Cardell LO. A preseason booster prolongs the increase of allergen specific IgG4 levels, after basic allergen intralymphatic immunotherapy, against grass pollen seasonal allergy. Allergy Asthma Clin Immunol 2020;16:31.
PUBMED | CROSSREF

72. Spina L, Weisskopf M, von Moos S, Graf N, Kündig TM, Senti G. Comparison of microneedles and adhesive-tape stripping in skin preparation for epicutaneous allergen delivery. Int Arch Allergy Immunol 2015;167:103-9.
PUBMED | CROSSREF

73. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. Eur J Immunol 2004;34:2100-9.
PUBMED | CROSSREF

74. Senti G, von Moos S, Tay F, Graf N, Johansen P, Kündig TM. Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. Allergy 2015;70:707-10.
PUBMED | CROSSREF

75. Esposito S, Isidori C, Pacitto A, Salvatori C, Sensi L, Frati F, et al. Epicutaneous immunotherapy in rhino-conjunctivitis and food allergies: a review of the literature. J Transl Med 2018;16:329.
PUBMED | CROSSREF

76. Wang Y, Kong Y, Wu MX. Innovative Systems to Deliver Allergen Powder for Epicutaneous Immunotherapy. Front Immunol 2021;12:647954.
PUBMED | CROSSREF

77. Slovick A, Douiri A, Muir R, Guerra A, Tsioulos K, Hay E, et al. Intradermal grass pollen immunotherapy increases T_H2 and IgE responses and worsens respiratory allergic symptoms. J Allergy Clin Immunol 2017;139:1830-1839.e13.
PUBMED | CROSSREF

78. Sola Martínez FJ, Barranco Jiménez RM, Martín García C, Senent Sánchez C, Blanco Guerra C, Fernández-Rivas M, et al. Intradermal Phleum pratense allergoid immunotherapy. Double-blind, randomized, placebo-controlled trial. Clin Exp Allergy 2020;50:1352-61.
PUBMED | CROSSREF

79. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. J Allergy Clin Immunol 2016;137:358-68.
PUBMED | CROSSREF

80. King TP, Hoffman D, Løwenstein H, Marsh DG, Platts-Mills TA, Thomas W. Allergen nomenclature. Allergy 1995;50:765-74.
PUBMED | CROSSREF

81. Spangfort MD, Larsen JN. Standardization of allergen-specific immunotherapy vaccines. Immunol Allergy Clin North Am 2006;26:191-206.
PUBMED | CROSSREF

82. Løwenstein H; International Union of Immunological Societies. Selection of reference preparation. IUIS reference preparation criteria. Arb Paul Ehrlich Inst Georg Speyer Haus Ferdinand Blum Inst Frankf AM 1987:75-8.
PUBMED

83. Lowenstein H. Physico-chemical and immunochemical methods for the control of potency and quality of allergenic extracts. In: Brede HO, Göing H, editors. Regulatory control and standardization of allergenic extracts. Stuttgart, Gustav Fischer; 1980. 122-32.

84. Pfaar O, Lou H, Zhang Y, Klimek L, Zhang L. Recent developments and highlights in allergen immunotherapy. Allergy 2018;73:2274-89.
PUBMED | CROSSREF

85. Lou H, Huang Y, Ouyang Y, Zhang Y, Xi L, Chu X, et al. Artemisia annua-sublingual immunotherapy for seasonal allergic rhinitis: a randomized controlled trial. Allergy 2020;75:2026-36.
PUBMED | CROSSREF

86. Zheng YW, Lai XX, Zhao DY, Zhang CQ, Chen JJ, Zhang L, et al. Indoor allergen levels and household distributions in nine cities across china. Biomed Environ Sci 2015;28:709-17.
PUBMED

87. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al.; AllerGen. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2) LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
PUBMED | CROSSREF

88. Nordic Council on Medicines. Registration of allergen preparations. Uppsala: NLN Publications; 1989.

89. Baer H, Godfrey H, Maloney CJ, Norman PS, Lichtenstein LM. The potency and antigen E content of commercially prepared ragweed extracts. J Allergy 1970;45:347-54.
PUBMED | CROSSREF

90. Baer H, Maloney CJ, Norman PS, Marsh DG. The potency and Group I antigen content of six commercially prepared grass pollen extracts. J Allergy Clin Immunol 1974;54:157-64.
PUBMED | CROSSREF

91. Cui YB, Cai HX, Zhou Y, Wang N, Yu LL, Yang L, et al. The Dermatophagoides farinae group 22 allergen: cloning and expression in Escherichia coli. Int Forum Allergy Rhinol 2015;5:794-800.
PUBMED | CROSSREF

92. Cui Y, Jiang Y, Ji Y, Zhou Y, Yu L, Wang N, et al. Cloning, expression, and analysis of a cDNA coding for the Dermatophagoides farinae group 21 (Der f 21) allergen. Am J Transl Res 2014;6:786-92.
PUBMED

93. Cui YB, Zhou Y, Wang N, Teng FX, Yu LL, Bian YH, et al. Expression, cloning, and IgE-binding of the full-length dust mite allergen Der f 8. Immunol Res 2014;60:60-8.
PUBMED | CROSSREF

94. Cui Y, Zhou Y, Wang Y, Ma G, Yang L. The group 10 allergen of Dermatophagoides farinae (Acari: Pyroglyphidae): cDNA cloning, sequence analysis, and expression in Escherichia coli BL21. J Med Entomol 2013;50:205-8.
PUBMED | CROSSREF

95. Cui Y, Zhou Y, Shi W, Ma G, Yang L, Wang Y, et al. Molecular cloning, expression, sequence analyses of dust mite allergen Der f 6 and its IgE-binding reactivity with mite allergic asthma patients in southeast China. Mol Biol Rep 2012;39:961-8.
PUBMED | CROSSREF

96. Cui Y, Zhou Y, Ma G, Yang L, Wang Y, Shi W. Cloning, bioinformatics analysis, and expression of the dust mite allergen Der f 5 of *Dermatophagoides farinae*. Braz J Med Biol Res 2012;45:746-52.
PUBMED | CROSSREF

97. Yu-bao C, Zhou Y, Weihong S, Guifang M, Yang L, Yungang W. Cloning, expression, and analysis of the group 2 allergen from *Dermatophagoides farinae* from China. An Acad Bras Cienc 2010;82:941-51.
PUBMED | CROSSREF

98. Cui YB, Cai HX, Zhou Y, Gao CX, Shi WH, Yu M, et al. Cloning, expression, and characterization of Der f 7, an allergen of *Dermatophagoides farinae* from China. J Med Entomol 2010;47:868-76.
PUBMED | CROSSREF

99. Cui YB, Cai HX, Li L, Zhou Y, Gao CX, Shi WH, et al. Cloning, sequence analysis and expression in E. coli of the group 3 allergen of *Dermatophagoides farinae*. Chin Med J (Engl) 2009;122:2657-61.
PUBMED

100. Sekerel BE, Sahiner UM, Bousquet J, Demoly P, Zuberbier T, Carlsen KH, et al. Practical guide to skin prick tests in allergy to aeroallergens: some concerns. Allergy 2012;67:442-3.
PUBMED | CROSSREF

101. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. Clin Transl Allergy 2013;3:3.
PUBMED | CROSSREF

102. Masse MS, Granger Vallée A, Chiriac A, Dhivert-Donnadieu H, Bousquet-Rouanet L, Bousquet PJ, et al. Comparison of five techniques of skin prick tests used routinely in Europe. Allergy 2011;66:1415-9.
PUBMED | CROSSREF

103. Wang J, Wu Y, Li J, Huang X, Zhu R. Eight aeroallergen skin extracts may be the optimal panel for allergic rhinitis patients in Central China. Int Arch Allergy Immunol 2017;173:193-8.
PUBMED | CROSSREF

104. Ménardo JL, Bousquet J, Rodière M, Astruc J, Michel FB. Skin test reactivity in infancy. J Allergy Clin Immunol 1985;75:646-51.
PUBMED | CROSSREF

105. Skassa-Brociek W, Manderscheid JC, Michel FB, Bousquet J. Skin test reactivity to histamine from infancy to old age. J Allergy Clin Immunol 1987;80:711-6.
PUBMED | CROSSREF

106. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy 2012;67:18-24.
PUBMED | CROSSREF

107. Wide L, Bennich H, Johansson SG. Diagnosis of allergy by an *in-vitro* test for allergen antibodies. Lancet 1967;2:1105-7.
PUBMED | CROSSREF

108. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J 2020;13:100080.
PUBMED | CROSSREF

109. Hamilton RG. Clinical laboratories worldwide need to report IgE antibody results on clinical specimens as analytical results and not use differential positive thresholds. J Allergy Clin Immunol 2015;136:811-2.
PUBMED | CROSSREF

110. Linden CC, Misiak RT, Wegienka G, Havstad S, Ownby DR, Johnson CC, et al. Analysis of allergen specific IgE cut points to cat and dog in the Childhood Allergy Study. Ann Allergy Asthma Immunol 2011;106:153-158.e2.
PUBMED | CROSSREF

111. Gelardi M, Iannuzzi L, Quaranta N, Landi M, Passalacqua G. NASAL cytology: practical aspects and clinical relevance. Clin Exp Allergy 2016;46:785-92.
PUBMED | CROSSREF

112. Heffler E, Landi M, Caruso C, Fichera S, Gani F, Guida G, et al. Nasal cytology: methodology with application to clinical practice and research. Clin Exp Allergy 2018;48:1092-106.
PUBMED | CROSSREF

113. Chen J, Zhou Y, Zhang L, Wang Y, Pepper AN, Cho SH, et al. Individualized treatment of allergic rhinitis according to nasal cytology. Allergy Asthma Immunol Res 2017;9:403-9.
PUBMED | CROSSREF

114. Bousquet J, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. J Allergy Clin Immunol 2012;130:1049-62.
PUBMED | CROSSREF

115. Lou HF, Huang YR, Wang CS, Wang XD, Zhao Y, Cao FF, et al. Long-term efficacy of house dust mite subcutaneous immunotherapy in allergic rhinitis patients. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2018;32:1627-31.
PUBMED | CROSSREF

116. Gelardi M, Incorvaia C, Passalacqua G, Quaranta N, Frati F. The classification of allergic rhinitis and its cytological correlate. Allergy 2011;66:1624-5.
PUBMED | CROSSREF

117. Canakcioglu S, Tahamiler R, Saritzali G, Alimoglu Y, Isildak H, Guvenc MG, et al. Evaluation of nasal cytology in subjects with chronic rhinitis: a 7-year study. Am J Otolaryngol 2009;30:312-7.
PUBMED | CROSSREF

118. Huggins KG, Brostoff J. Local production of specific IgE antibodies in allergic-rhinitis patients with negative skin tests. Lancet 1975;2:148-50.
PUBMED | CROSSREF

119. Liang MJ, Fu QL, Jiang HY, Chen FH, Chen D, Chen DH, et al. Immune responses to different patterns of exposure to ovalbumin in a mouse model of allergic rhinitis. Eur Arch Otorhinolaryngol 2016;273:3783-8.
PUBMED | CROSSREF

120. Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. Clin Exp Allergy 2003;33:1374-9.
PUBMED | CROSSREF

121. Morse JC, Li P, Ely KA, Shilts MH, Wannemuehler TJ, Huang LC, et al. Chronic rhinosinusitis in elderly patients is associated with an exaggerated neutrophilic proinflammatory response to pathogenic bacteria. J Allergy Clin Immunol 2019;143:990-1002.e6.
PUBMED | CROSSREF

122. Meng Y, Lou H, Wang Y, Wang C, Zhang L. The use of specific immunoglobulin E in nasal secretions for the diagnosis of allergic rhinitis. Laryngoscope 2018;128:E311-5.
PUBMED | CROSSREF

123. Tao XY, Ng CL, Chen D, Lin ZB, Wu SL, Liang MJ, et al. Clinical characteristics and allergen sensitization patterns of patients with local allergic rhinitis in Southern China. Int Arch Allergy Immunol 2018;175:107-13.
PUBMED | CROSSREF

124. Meng Y, Wang Y, Lou H, Wang K, Meng N, Zhang L, et al. Specific immunoglobulin E in nasal secretions for the diagnosis of local allergic rhinitis. Rhinology 2019;57:313-20.
PUBMED | CROSSREF

125. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: a practice parameter update. J Allergy Clin Immunol 2020;146:721-67.
PUBMED | CROSSREF

126. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Allergy 2017;72:1597-631.
PUBMED | CROSSREF

127. Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G, et al. Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. Pediatr Allergy Immunol 2017;28:18-29.
PUBMED | CROSSREF

128. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol 2017;28:728-45.
PUBMED | CROSSREF

129. Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Subspecialty Group of Rhinology, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association. Chinese guidelines for diagnosis and treatment of allergic rhinitis.

Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2016;51:6-24.
PUBMED | CROSSREF

130. Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, et al. EAACI allergen immunotherapy user's guide. Pediatr Allergy Immunol 2020;31 Suppl 25:1-101.
131. Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, et al. Japanese guidelines for allergic rhinitis 2020. Allergol Int 2020;69:331-45.
PUBMED | CROSSREF
132. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy 2018;73:765-98.
PUBMED | CROSSREF
133. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.
PUBMED | CROSSREF
134. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31:1392-7.
PUBMED | CROSSREF
135. Des Roches A, Paradis L, Menardo JL, Bouges S, Daurés JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3.
PUBMED | CROSSREF
136. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. Int Arch Allergy Immunol 2012;157:288-98.
PUBMED | CROSSREF
137. Rodriguez Del Rio P, Vidal C, Just J, Tabar AI, Sanchez-Machin I, Eberle P, et al. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a paediatric assessment. Pediatr Allergy Immunol 2017;28:60-70.
PUBMED | CROSSREF
138. Oykhman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. Allergy Asthma Clin Immunol 2015;11:31.
PUBMED | CROSSREF
139. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127 Suppl:S1-55.
PUBMED | CROSSREF
140. Pitsios C, Demoly P, Bilò MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy 2015;70:897-909.
PUBMED | CROSSREF
141. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. Allergy 2012;67:741-3.
PUBMED | CROSSREF
142. American Academy of Allergy Asthma & Immunology (AAAAI). Suggestions or considerations for resuming practices [Internet]. Milwaukee (WI): AAAAI; 2022. Available from: www.aaaai.org.
143. Jakob T, Klimek L. Allergologie in Zeiten von Covid-19. Allergo J 2020;29:3.
PUBMED | CROSSREF
144. Klimek L, Pfaar O, Worm M, Bergmann KC, Bieber T, Buhl R, et al. Allergen-Immuntherapie in der aktuellen Covid-19-Pandemie. Allergo J 2020;29:17-25.
PUBMED | CROSSREF
145. American Academy of Otolaryngology–Head and Neck Surgery. Allergic reactions related to COVID-19 vaccination in allergic patients. American Academy of Otolaryngology-Head and Neck Surgery: Joint Statement by the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) and the American Academy of Otolaryngic Allergy (AAOA) [Internet]. Alexandria (VA): American Academy of Otolaryngology–Head and Neck Surgery; [cited 2020 Dec 25]. Available from: https://www.entnet.org/content/allergic-reactions-related-covid-19-vaccinations-allergic-patients.
146. Klimek L, Bergmann KC, Brehler R, Pfützner W, Zuberbier T, Hartmann K, et al. Practical handling of allergic reactions to COVID-19 vaccines: a position paper from German and Austrian Allergy Societies AeDA, DGAKI, GPA and ÖGAI. Allergo J Int 2021;30:79-95.
PUBMED | CROSSREF

147. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet 2011;378:2112-22.
PUBMED | CROSSREF

148. Song Y, Long J, Wang T, Xie J, Wang M, Tan G. Long-term efficacy of standardised specific subcutaneous immunotherapy in children with persistent allergic rhinitis due to multiple allergens including house dust mites. J Laryngol Otol 2018;132:230-5.
PUBMED | CROSSREF

149. Qi S, Chen H, Huang N, Li W, Liu G, Wang Y, et al. Early intervention improves clinical responses to house dust mite immunotherapy in allergic rhinitis patients. Int Arch Allergy Immunol 2016;171:234-40.
PUBMED | CROSSREF

150. Zhao X, Wu H, Lin L, Liu Q, Li X, Luo B. Effect and safety analysis of Allergovit standardized mite allergen immunotherapy in patients with allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2013;27:1128-31.
PUBMED

151. Song W, Lin X, Chai R. Efficacy evaluation of standardized dust mite allergen specific immunotherapy to patients of allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2014;28:300-2.
PUBMED

152. Xiao SF, Wang QH. Effect of immunotherapy on house dust mite allergen-specific IgG1 and igG4 antibodies in nasal secretion for patients with perennial allergic rhinitis. Zhonghua Er Bi Yan Hou Ke Za Zhi 2004;39:725-9.
PUBMED

153. Roche AM, Wise SK. Subcutaneous immunotherapy. Int Forum Allergy Rhinol 2014;4 Suppl 2:S51-4.
PUBMED | CROSSREF

154. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998;102:558-62.
PUBMED | CROSSREF

155. Zhang L, Wang C, Han D, Wang X, Zhao Y, Liu J. Comparative study of cluster and conventional immunotherapy schedules with dermatophagoides pteronyssinus in the treatment of persistent allergic rhinitis. Int Arch Allergy Immunol 2009;148:161-9.
PUBMED | CROSSREF

156. Jiang Z, Xiao H, Zhang H, Liu S, Meng J. Comparison of adverse events between cluster and conventional immunotherapy for allergic rhinitis patients with or without asthma: a systematic review and meta-analysis. Am J Otolaryngol 2019;40:102269.
PUBMED | CROSSREF

157. Tabar AI, Echechipía S, García BE, Olaguibel JM, Lizaso MT, Gómez B, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. J Allergy Clin Immunol 2005;116:109-18.
PUBMED | CROSSREF

158. Bao Y, Chen J, Cheng L, Guo Y, Hong S, Kong W, et al. Chinese Guideline on allergen immunotherapy for allergic rhinitis. J Thorac Dis 2017;9:4607-50.
PUBMED | CROSSREF

159. Buczyłko K, van der Werf JF, Boot D, van Ree R. Accelerated up-dosing of subcutaneous immunotherapy with a registered allergoid birch pollen preparation. Int Arch Allergy Immunol 2017;172:183-6.
PUBMED | CROSSREF

160. Klimek L, Uhlig J, Mösges R, Rettig K, Pfaar O. A high polymerized grass pollen extract is efficacious and safe in a randomized double-blind, placebo-controlled study using a novel up-dosing cluster-protocol. Allergy 2014;69:1629-38.
PUBMED | CROSSREF

161. Pospischil IM, Kagerer M, Cozzio A, Angelova-Fischer I, Guenova E, Ballmer-Weber B, et al. Comparison of the safety profiles of 3 different hymenoptera venom immunotherapy protocols: a retrospective 2-center study of 143 patients. Int Arch Allergy Immunol 2020;181:783-9.
PUBMED | CROSSREF

162. Fajt ML, Rosenberg SL, Yecies E, Traister RS, Petrov AA. A 10-year experience of a novel and safe modified environmental rush immunotherapy protocol. Allergy Asthma Proc 2017;38:309-16.
PUBMED | CROSSREF

163. Lee JH, Choi JH, Jeong KB, Lee SJ, Lee MK, Lee WY, et al. Safety and utility of rush immunotherapy with aqueous allergen extracts for treatment of respiratory allergies. J Korean Med Sci 2021;36:e18.
PUBMED | CROSSREF

164. Stock R, Fischer T, Aßemus K, Zoeller N, Ackermann H, Kaufmann R, et al. Safety and tolerability of venom immunotherapy: evaluation of 581 rush- and ultra-rush induction protocols (safety of rush and ultra-rush venom immunotherapy). World Allergy Organ J 2020;14:100496.
PUBMED | CROSSREF

165. Tanaka Y, Okafuji I, Narabayashi S, Tsuruta S. Safety and efficacy of one-year rush subcutaneous immunotherapy in Japanese children, using house dust extract. Arerugi 2015;64:1160-8.
PUBMED | CROSSREF

166. Tanaka Y, Okafuji I, Omae S, Mitobe Y, Doi K, Tsuruta S. Difference between standardized mite antigen and house dust extract in rush subcutaneous immunotherapy for children. Arerugi 2019;68:681-90.
PUBMED | CROSSREF

167. Temiño VM, Wu P, Konig J, Fahrenholz JM. Safety of multiple aeroallergen rush immunotherapy using a modified schedule. Allergy Asthma Proc 2013;34:255-60.
PUBMED | CROSSREF

168. Gao P, Yu W, Zhou Y, Zhu W, Zhu Z, Jiang Y, et al. Safety comparison of omalizumab and glucocorticoid in rush allergen immunotherapy. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2020;34:610-4.
PUBMED

169. Qiu Q, Xu M, Lu C, Chen J, Chen S, Kong W, et al. Safety and efficacy of rush allergen-specific immunotherapy in Chinese allergic rhinitis patients. Int J Immunopathol Pharmacol 2016;29:720-5.
PUBMED | CROSSREF

170. Zhu XH, Huang Y, Jiang YL. Analysis of changes in serological factors in the dose-increasing phase of allergic rhinitis rush immunotherapy. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2019;33:36-40.
PUBMED

171. National Center for Immunization and Respiratory Diseases. General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-64.
PUBMED

172. Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Subspecialty Group of Rhinology, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association. Expert consensus on allergen specific immunotherapy of allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;46:976-80.
PUBMED

173. Solelhac G, Charpin D. Management of allergic rhinitis. F1000Prime Rep 2014;6:94.
PUBMED | CROSSREF

174. Pan L, Liao B, Guo CL, Liu JX, Wang H, Long XB, et al. Inflammatory features and predictors for postsurgical outcomes in patients with nasal polyps stratified by local and systemic eosinophilia. Int Forum Allergy Rhinol 2021;11:846-56.
PUBMED | CROSSREF

175. Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. Clin Exp Allergy 2011;41:1177-200.
PUBMED | CROSSREF

176. Haccuria A, Van Muylem A, Malinovschi A, Doan V, Michils A. Small airways dysfunction: the link between allergic rhinitis and allergic asthma. Eur Respir J 2018;51:1701749.
PUBMED | CROSSREF

177. Paiva Ferreira LK, Paiva Ferreira LA, Monteiro TM, Bezerra GC, Bernardo LR, Piuvezam MR. Combined allergic rhinitis and asthma syndrome (CARAS). Int Immunopharmacol 2019;74:105718.
PUBMED | CROSSREF

178. Bousquet J, Pfaar O, Togias A, Schünemann HJ, Ansotegui I, Papadopoulos NG, et al. 2019 ARIA Care pathways for allergen immunotherapy. Allergy 2019;74:2087-102.
PUBMED | CROSSREF

179. Lin J, Su N, Liu G, Yin K, Zhou X, Shen H, et al. The impact of concomitant allergic rhinitis on asthma control: a cross-sectional nationwide survey in China. J Asthma 2014;51:34-43.
PUBMED | CROSSREF

180. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: executive summary and rationale for key changes. Eur Respir J 2021;59:2102730.
PUBMED | CROSSREF

181. Arroabarren E, Tabar AI, Echechipía S, Cambra K, García BE, Alvarez-Puebla MJ. Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. Pediatr Allergy Immunol 2015;26:34-41.
PUBMED | CROSSREF

182. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. J Allergy Clin Immunol 2015;136:1511-6.
PUBMED | CROSSREF

183. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. Allergy 2017;72:1825-48.
PUBMED | CROSSREF

184. Global Initiative for Asthma. Global strategy for asthma management and prevention [Internet]. Fontana (WI): Global Initiative for Asthma; 2021 [cited 2021 Nov 1]. Available from: www.ginasthma.org.

185. Pawankar R, Walter C, Holgate ST, Lockey RF. WAO, white book on allergy. Milwaukee (WI): World Allergy Organization; 2012. 55-8.

186. Graffigna G, Barello S. Innovating healthcare in the era of patient engagement: challenges, opportunities & new trends. In: Graffigna G, Barello S, Triberti S, editors. Patient engagement: a consumer-centered model to innovate healthcare. Berlin: DeGruyter Open; 2015. 10-20.

187. Wang C, Zhang L. Specific immunotherapy for allergic rhinitis in children. Curr Opin Otolaryngol Head Neck Surg 2014;22:487-94.
PUBMED | CROSSREF

188. Pizzulli A, Perna S, Florack J, Pizzulli A, Giordani P, Tripodi S, et al. The impact of telemonitoring on adherence to nasal corticosteroid treatment in children with seasonal allergic rhinoconjunctivitis. Clin Exp Allergy 2014;44:1246-54.
PUBMED | CROSSREF

189. Huang Y, Wang C, Cao F, Zhao Y, Lou H, Zhang L. Comparison of long-term efficacy of subcutaneous immunotherapy in pediatric and adult patients with allergic rhinitis. Allergy Asthma Immunol Res 2019;11:68-78.
PUBMED | CROSSREF

190. Peng H, Li CW, Lin ZB, Li TY. Long-term efficacy of specific immunotherapy on house dust mite-induced allergic rhinitis in China. Otolaryngol Head Neck Surg 2013;149:40-6.
PUBMED | CROSSREF

191. Guo JF, Liu P, Wu HQ, Lin LL, Liu Z, Xiong BB. Effect of specific immunotherapy on the psychological health level and quality of life in patients with allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2016;30:712-4.
PUBMED

192. Huang R, Qin R, Hu Q, Zhu Z, Liu Y, Luo T, et al. Effect of *Dermatophagoides pteronyssinus* immunotherapy on upper and lower airway eosinophilic inflammatory response to nasal allergen challenge. Allergy Asthma Immunol Res 2020;12:844-58.
PUBMED | CROSSREF

193. Wang Z, Peng H, Rao K. The secondary prevention effect and influence on serum sIgG4, IL-27 and IL-33 levels of subcutaneous immunotherapy in children with allergic rhinitis and cough variant asthma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2020;34:793-8.
PUBMED

194. Huang Y, Wang C, Wang X, Zhang L, Lou H. Efficacy and safety of subcutaneous immunotherapy with house dust mite for allergic rhinitis: a meta-analysis of randomized controlled trials. Allergy 2019;74:189-92.
PUBMED | CROSSREF

195. Zhu ZC, Qiu QH, Chen Z, Huang HM, Han H, Chen JJ, et al. Analysis of the efficacy and compliance of conventional immunotherapy and rush immunotherapy in patients with allergic rhinitis. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2018;32:81-6.
PUBMED | CROSSREF

196. Sahin E, Dizdar D, Dinc ME, Cirik AA. Long-term effects of allergen-specific subcutaneous immunotherapy for house dust mite induced allergic rhinitis. J Laryngol Otol 2017;131:997-1001.
PUBMED | CROSSREF

197. Fan Q, Liu X, Gao J, Huang S, Ni L. Comparative analysis of cluster versus conventional immunotherapy in patients with allergic rhinitis. Exp Ther Med 2017;13:717-22.
PUBMED | CROSSREF

198. Yu J, Zhong N, Luo Q, Liu Y, Yi H, Ye J, et al. Early efficacy analysis of cluster and conventional immunotherapy in patients with allergic rhinitis. Ear Nose Throat J 2021;100:378-85.
PUBMED | CROSSREF

199. Augé J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A, et al. EAACI Position paper on the standardization of nasal allergen challenges. Allergy 2018;73:1597-608.
PUBMED | CROSSREF

200. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. J Allergy Clin Immunol 2017;140:1485-98.
PUBMED | CROSSREF

201. Huang Y, Wang C, Lin X, Lou H, Cao F, Li W, et al. Association between component-resolved diagnosis of house dust mite and efficacy of allergen immunotherapy in allergic rhinitis patients. Clin Transl Allergy 2019;9:64.
PUBMED | CROSSREF

202. Alpan O, Layhadi JA, Ulrik Sønder S, Li H, Shamji MH. Basophil activation test: A diagnostic, predictive and monitoring assay for allergen immunotherapy. Allergy 2021;76:1321-4.
PUBMED | CROSSREF

203. Schmid JM, Würtzen PA, Siddhuraj P, Jogdand P, Petersen CG, Dahl R, et al. Basophil sensitivity reflects long-term clinical outcome of subcutaneous immunotherapy in grass pollen-allergic patients. Allergy 2021;76:1528-38.
PUBMED | CROSSREF

204. Xie S, Fan R, Tang Q, Cai X, Zhang H, Wang F, et al. Identification of robust biomarkers for early predicting efficacy of subcutaneous immunotherapy in children with house dust mite-induced allergic rhinitis by multiple cytokine profiling. Front Immunol 2022;12:805404.
PUBMED | CROSSREF

205. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. Allergy 2017;72:1156-73.
PUBMED | CROSSREF

206. Ma TT, Cao MD, Yu RL, Shi HY, Yan WJ, Liu JG, et al. Leukotriene A_4 hydrolase is a candidate predictive biomarker for successful allergen immunotherapy. Front Immunol 2020;11:559746.
PUBMED | CROSSREF

207. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 2010;125:131-138.e1-7.
PUBMED | CROSSREF

208. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001;31:1295-302.
PUBMED | CROSSREF

209. Bush RK. Advances in allergen immunotherapy in 2015. J Allergy Clin Immunol 2016;138:1284-91.
PUBMED | CROSSREF

210. Shin YS, Jung JW, Park JW, Choi JH, Kwon JW, Lee S, et al. Clinical efficacy of allergen-specific immunotherapy from patient and physician perspectives. Yonsei Med J 2019;60:446-53.
PUBMED | CROSSREF

211. Liu Z, Lu H, Feng X, Hu L, Wang J, Yu H. Predictive methods for efficacy of house dust mite subcutaneous immunotherapy in allergic rhinitis patients: a prospective study in a Chinese population. Int Forum Allergy Rhinol 2020;10:314-9.
PUBMED | CROSSREF

212. Uriarte SA, Sastre J. Subcutaneous immunotherapy with high-dose cat and dog extracts: a real-life study. J Investig Allergol Clin Immunol 2020;30:169-74.
PUBMED | CROSSREF

213. Uriarte SA, Grönlund H, Wintersand A, Bronge J, Sastre J. Clinical and immunologic changes due to subcutaneous immunotherapy with cat and dog extracts using an ultrarush up-dosing phase: a real-life study. J Investig Allergol Clin Immunol 2022;32:133-40.
PUBMED | CROSSREF

214. Kepil Özdemir S, Sin BA, Güloğlu D, İkincioğulları A, Gençtürk Z, Mısırlıgil Z. Short-term preseasonal immunotherapy: is early clinical efficacy related to the basophil response? Int Arch Allergy Immunol 2014;164:237-45.
PUBMED | CROSSREF

215. Shi HY, Pan C, Ma TT, Chen YL, Yan WJ, Liu JG, et al. Clinical efficacy evaluation of 1-year subcutaneous immunotherapy for *Artemisia sieversiana* pollen allergic rhinitis by serum metabolomics. Front Pharmacol 2020;11:305.
PUBMED | CROSSREF

216. Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Subspecialty Group of Rhinology and Pediatrics, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association; Editorial Board of Chinese Journal of Pediatrics. Guidelines for diagnosis and treatment of pediatric allergic rhinitis (2010, Chongqing). Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;46:7-8.
PUBMED

217. Wang CS, Zhang W, Wang XD, Xi L, Ouyang YH, Zhao Y, et al. Clinical efficacy and immunological changes in children with allergic rhinitis receiving specific immunotherapy with *Dermatophagoides pteronyssinus*. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;46:36-9.
PUBMED

218. Arasi S, Pajno GB, Panasiti I, Sandoval M, Alvaro-Lozano M. Allergen Immunotherapy in children with respiratory allergic diseases. Minerva Pediatr 2020;72:343-57.
PUBMED | CROSSREF

219. Skorokhodkina OV, Arkhipova SA, Luntsov AV, Zaynetdinova GM, Volkova DA. Assessment of efficacy of allergen immunotherapy in children and adults with allergic rhinitis. Vestn Otorinolaringol 2020;85:60-5.
PUBMED | CROSSREF

220. Zhao D, Lai X, Tian M, Jiang Y, Zheng Y, Gjesing B, et al. The functional IgE-blocking factor induced by allergen-specific immunotherapy correlates with IgG4 antibodies and a decrease of symptoms in house dust mite-allergic children. Int Arch Allergy Immunol 2016;169:113-20.
PUBMED | CROSSREF

221. Wang CS, Wang XD, Zhang W, She WY, Xi L, Ouyang YH, et al. Long-term efficacy of *Dermatophagoides pteronyssinus* immunotherapy in patients with allergic rhinitis: a 3-year prospective study. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012;47:804-8.
PUBMED

222. Penagos M, Eifan AO, Durham SR, Scadding GW. Duration of allergen immunotherapy for long-term efficacy in allergic rhinoconjunctivitis. Curr Treat Options Allergy 2018;5:275-90.
PUBMED | CROSSREF

223. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.
PUBMED | CROSSREF

224. Cappella A, Durham SR. Allergen immunotherapy for allergic respiratory diseases. Hum Vaccin Immunother 2012;8:1499-512.
PUBMED | CROSSREF

225. Kramer MS, Matush L, Bogdanovich N, Dahhou M, Platt RW, Mazer B. The low prevalence of allergic disease in Eastern Europe: are risk factors consistent with the hygiene hypothesis? Clin Exp Allergy 2009;39:708-16.
PUBMED | CROSSREF

226. Mustafa SS, Vadamalai K, Bingemann T, Ramsey A. Efficacy of epinephrine and diphenhydramine rinses in decreasing local reactions to subcutaneous aeroallergen immunotherapy. Allergy Asthma Proc 2020;41:52-8.
PUBMED | CROSSREF

227. Zhang W, Deng Y, Tong H, Xiang R, Chen S, Kong Y, et al. Adverse reactions to subcutaneous immunotherapy in patients with allergic rhinitis, a real-world study. Eur Arch Otorhinolaryngol 2021;278:4353-60.
PUBMED | CROSSREF

228. Coop CA. Local reactions from subcutaneous allergen immunotherapy. Immunotherapy 2013;5:1339-45.
PUBMED | CROSSREF

229. Nelson HS. Effect of preservatives and conditions of storage on the potency of allergy extracts. J Allergy Clin Immunol 1981;67:64-9.
PUBMED | CROSSREF

230. Van Metre TE Jr, Rosenberg GL, Vaswani SK, Ziegler SR, Adkinson NF. Pain and dermal reaction caused by injected glycerin in immunotherapy solutions. J Allergy Clin Immunol 1996;97:1033-9.
PUBMED | CROSSREF

231. Yang Y, Ma D, Huang N, Li W, Jiang Q, Wang Y, et al. Safety of house dust mite subcutaneous immunotherapy in preschool children with respiratory allergic diseases. Ital J Pediatr 2021;47:101.
PUBMED | CROSSREF

232. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization systemic allergic reaction grading system: is a modification needed? J Allergy Clin Immunol Pract 2017;5:58-62.e5.
PUBMED | CROSSREF

233. Epstein TG, Liss GM, Berendts KM, Bernstein DI. AAAAI/ACAAI Subcutaneous Immunotherapy Surveillance Study (2013–2017): fatalities, infections, delayed reactions, and use of epinephrine autoinjectors. J Allergy Clin Immunol Pract 2019;7:1996-2003.e1.
PUBMED | CROSSREF

234. Shen Y, Hong S, Zhang M, Ke X. Observation of systemic adverse reactions by specific immunotherapy and analysis of risk factors in allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2017;52:801-5.
PUBMED | CROSSREF

235. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. Effect of 1-year specific immunotherapy with standardized house dust mite vaccine on mild to moderate allergic asthmatic patients. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:679-87.
PUBMED

236. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010;125:569-74, 574.e1-574.e7.
PUBMED | CROSSREF

237. Copenhaver CC, Parker A, Patch S. Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice. Ann Allergy Asthma Immunol 2011;107:441-7.
PUBMED | CROSSREF

238. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract 2014;2:161-7.
PUBMED | CROSSREF

239. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006;117:169-75.
PUBMED | CROSSREF

240. Dhamija Y, Epstein TE, Bernstein DI. Systemic allergic reactions and anaphylaxis associated with allergen immunotherapy. Immunol Allergy Clin North Am 2022;42:105-19.
PUBMED | CROSSREF

241. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E, et al. Standards for practical allergen-specific immunotherapy. Allergy 2006;61 Suppl 82:1-20.
PUBMED | CROSSREF

242. Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. Ann Allergy Asthma Immunol 2010;104:530-5.
PUBMED | CROSSREF

243. Vidal C, Rodríguez Del Río P, Gude F, Casale T, Cox L, Just J, et al. Comparison of international systemic adverse reactions due to allergen immunotherapy. J Allergy Clin Immunol Pract 2019;7:1298-1305.e3.
PUBMED | CROSSREF

244. Confino-Cohen R, Goldberg A. Allergen immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study. Ann Allergy Asthma Immunol 2010;104:73-8.
PUBMED | CROSSREF

245. Scranton SE, Gonzalez EG, Waibel KH. Incidence and characteristics of biphasic reactions after allergen immunotherapy. J Allergy Clin Immunol 2009;123:493-8.
PUBMED | CROSSREF

246. Dong X, Huang N, Li W, Hu L, Wang X, Wang Y, et al. Systemic reactions to dust mite subcutaneous immunotherapy: a 3-year follow-up study. Allergy Asthma Immunol Res 2016;8:421-7.
PUBMED | CROSSREF

247. Feng M, Zeng X, Li J. House dust mite subcutaneous immunotherapy in Chinese patients with allergic asthma and rhinitis. J Thorac Dis 2019;11:3616-25.
PUBMED | CROSSREF

248. Kannan JA, Epstein TG. Immunotherapy safety: what have we learned from surveillance surveys? Curr Allergy Asthma Rep 2013;13:381-8.
PUBMED | CROSSREF

249. Kim L, Nevis I, Potts R, Eeuwes C, Dominic A, Kim HL. Patients on subcutaneous allergen immunotherapy are at risk of intramuscular injections. Allergy Asthma Clin Immunol 2014;10:22.
PUBMED | CROSSREF

250. Lieberman P. The risk and management of anaphylaxis in the setting of immunotherapy. Am J Rhinol Allergy 2012;26:469-74.
PUBMED | CROSSREF

251. Xiang L, Liu F, Zhi L, Jiang W, Liu C, Xie H, et al. Safety of semi-depot house dust mite allergen extract in children and adolescents with allergic rhinitis and asthma. Immunotherapy 2021;13:227-39.
PUBMED | CROSSREF

252. Li X, Wang X, Lin X, Xu G, Tao Z, Jiang W, et al. Semi-depot house-dust mite allergen extract for Chinese with allergic rhinitis and asthma. Am J Rhinol Allergy 2016;30:201-8.
PUBMED | CROSSREF

253. Liu JL, Ning WX, Li SX, Xu YC, Wu L, Wang YS, et al. The safety profile of subcutaneous allergen immunotherapy in children with asthma in Hangzhou, East China. Allergol Immunopathol (Madr) 2017;45:541-8.
PUBMED | CROSSREF

254. Bao Y, Chen J, Cheng L, Guo Y, Hong S, Kong W, et al. Chinese Guideline on allergen immunotherapy for allergic rhinitis. J Thorac Dis 2017;9:4607-50.
PUBMED | CROSSREF

255. Wang CS, Zhang W, Wang XD, Xi L, Ouyang YH, Zhao Y, et al. Comparative study on cluster and conventional immunotherapy with *Dermatophagoides pteronyssinus* in patients with allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2011;46:981-5.
PUBMED

256. Feng S, Xu Y, Ma R, Sun Y, Luo X, Li H. Cluster subcutaneous allergen specific immunotherapy for the treatment of allergic rhinitis: a systematic review and meta-analysis. PLoS One 2014;9:e86529.
PUBMED | CROSSREF

257. Yu J, Zhong N, Luo Q, Liu Y, Yi H, Ye J, et al. Early efficacy analysis of cluster and conventional immunotherapy in patients with allergic rhinitis. Ear Nose Throat J 2021;100:378-85.
PUBMED | CROSSREF

258. Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.
PUBMED | CROSSREF

259. Nagata M, Yamamoto H, Tabe K, Kimura I, Houya I, Kuramitsu K, et al. Effect of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: changes in *in vivo* and *in vitro* responses to HDM. Intern Med 1993;32:702-9.
PUBMED | CROSSREF

260. Hejjaoui A, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. J Allergy Clin Immunol 1992;89:925-33.
PUBMED | CROSSREF

261. Cox L. Accelerated immunotherapy schedules: review of efficacy and safety. Ann Allergy Asthma Immunol 2006;97:126-37.
PUBMED | CROSSREF

262. Kim ME, Kim JE, Sung JM, Lee JW, Choi GS, Nahm DH. Safety of accelerated schedules of subcutaneous allergen immunotherapy with house dust mite extract in patients with atopic dermatitis. J Korean Med Sci 2011;26:1159-64.
PUBMED | CROSSREF

263. Lee SH, Kim ME, Shin YS, Ye YM, Park HS, Nahm DH. Safety of ultra-rush schedule of subcutaneous allergen immunotherapy with house dust mite extract conducted in an outpatient clinic in patients with atopic dermatitis and allergic rhinitis. Allergy Asthma Immunol Res 2019;11:846-55.
PUBMED | CROSSREF

264. Smits WL, Giese JK, Letz KL, Inglefield JT, Schlie AR. Safety of rush immunotherapy using a modified schedule: a cumulative experience of 893 patients receiving multiple aeroallergens. Allergy Asthma Proc 2007;28:305-12.
PUBMED | CROSSREF

265. Kowalski ML, Ansotegui I, Aberer W, Al-Ahmad M, Akdis M, Ballmer-Weber BK, et al. Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement. World Allergy Organ J 2016;9:33.
PUBMED | CROSSREF

266. Zhang W, Lin C, Sampath V, Nadeau K. Impact of allergen immunotherapy in allergic asthma. Immunotherapy 2018;10:579-93.
PUBMED | CROSSREF

267. Hossenbaccus L, Linton S, Garvey S, Ellis AK. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol 2020;16:39.
PUBMED | CROSSREF

268. Chen J, Li B, Zhao Y, Zhang Q, Wan L, Liu J, et al. A prospective multicenter study of systemic reactions in standardized specific immunotherapy for allergic rhinitis in China. Am J Rhinol Allergy 2014;28:e40-4.
PUBMED | CROSSREF

269. Proctor T, Morrough E, Fenske O, Allatt S, Hughes SM, Sharma V, et al. Impact on quality of life and safety of sublingual and subcutaneous immunotherapy in children with severe house dust mite and pollen-associated allergic rhinoconjunctivitis. Clin Transl Allergy 2020;10:10.
PUBMED | CROSSREF

270. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69:1026-45.
PUBMED | CROSSREF

271. Group TCARCR. Chinese consensus on allergen specific subcutaneous immunotherapy in allergic rhinitis. Chin Arch Otolaryngol Head Neck Surg 2015:379-404.

272. de Silva D, Singh C, Muraro A, Worm M, Alviani C, Cardona V, et al. Diagnosing, managing and preventing anaphylaxis: Systematic review. Allergy 2021;76:1493-506.
PUBMED | CROSSREF

273. Zhang Y, Zhang L. Management practice of allergic rhinitis in china during the COVID-19 pandemic. Allergy Asthma Immunol Res 2020;12:738-42.
PUBMED | CROSSREF

274. China Association for Promotion of Health Science and Technology Child Allergy Professional Committee. Expert recommendations on the management of childhood bronchial asthma during the novel coronavirus pneumonia epidemic. J Thorac Dis 2020;12:4391-7.
PUBMED | CROSSREF

275. Zhou S, Liu Y, Xue J, Tang J, Yu Q, Qu S, et al. Sustained impact of subcutaneous immunotherapy among patients with allergic rhinitis who experienced treatment delay due to the COVID-19 pandemic: a multicenter, two-arm, real-world study. Clin Transl Allergy 2022;12:e12122.
PUBMED | CROSSREF

276. Xi L, Wang C, Gao Y, Zhang Y, Zhang L. Comparative study of novel dosing schedules for interrupted immunotherapy for allergic rhinitis. Clin Transl Allergy 2022;12:e12147.
PUBMED | CROSSREF

277. Chang C, Zhang L, Dong F, Liang Y, Chen Y, Shang Y, et al. Asthma control, self-management, and healthcare access during the COVID-19 epidemic in Beijing. Allergy 2021;76:586-8.
PUBMED | CROSSREF