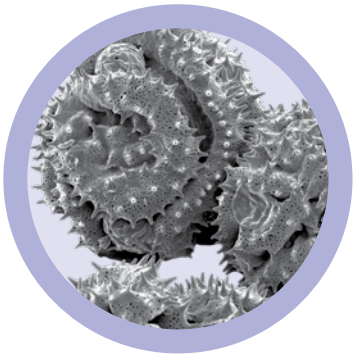
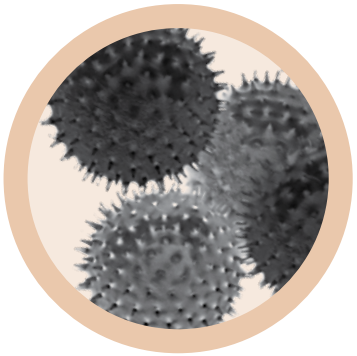
IgE-mediated allergic diseases

Pathophysiology, Diagnosis, Therapy

allergopharma



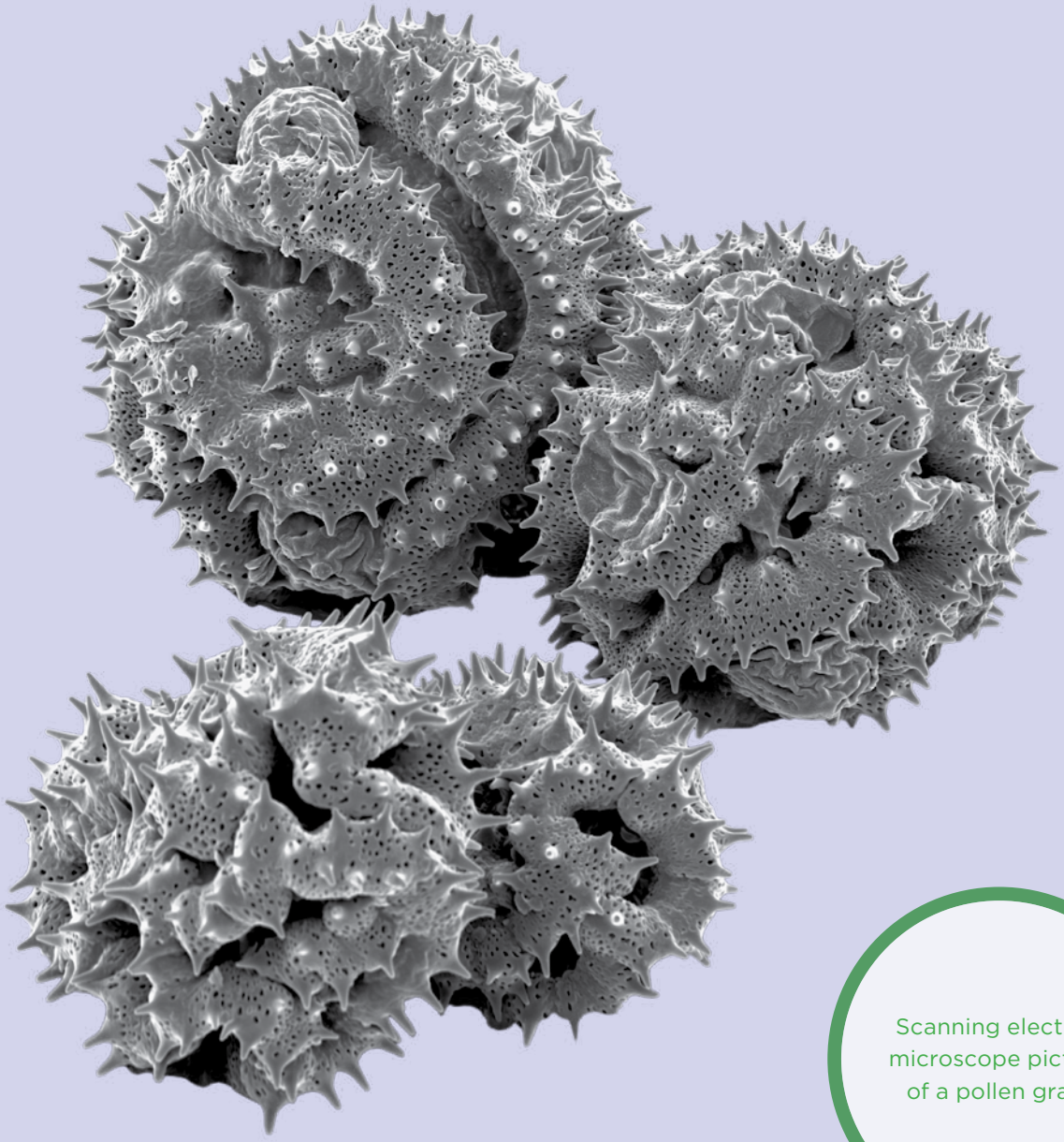


GLOSSARY

Until now, the terminology for allergic diseases has not been applied uniformly, which has hindered the provision of optimal patient care as well as scientific research. In order to ease communication between clinicians, the European Academy of Allergology and Clinical Immunology (EAACI) and the World Allergy Organization (WAO) have recommended a joint nomenclature based on the mechanisms underlying the various reactions [1–3].

Terminology	Definitions
Allergen Immunotherapy	(AIT (formerly SIT)): the only available treatment that targets the underlying pathophysiology and has a modifying effect on the allergic disease. Through the administration of allergen extracts, specific blocking antibodies, tolerance-inducing cells and chemical messengers are activated, which prevent a further strengthening of the immune response triggered by the allergen, block the specific immune response and reduce the inflammatory reaction in the tissue. This causal, immunomodulatory therapy can be administered subcutaneously (SCIT) or sublingually (SLIT). [4]
Allergy	according to EAACI/WAO: hypersensitivity reaction provoked by immunological mechanisms. It may be antibody- or cell-mediated, though IgE antibodies are involved in most cases **(IgE-mediated allergies)**. These should be distinguished from the **"non-IgE-mediated allergic reactions"**, in which the antibody responsible belongs to the IgG isotype. [1–3]
Allergic asthma	according to EAACI/WAO: basic term for asthma for which immunological mechanisms are an underlying cause. If IgE-mediated reactions have been diagnosed, the term **"IgE-mediated asthma"** is appropriate [2]. The IgE antibodies can initiate both, an immediate and a delayed asthma reaction. For both reactions, however, as in other allergic diseases as well, T cell associated reactions appear to be important. Depending on the duration of the symptoms, the asthma should be defined as **intermittent** or **persistent**. [1–3]
Asthma	according to GINA (Global Initiative for Asthma): heterogeneous, chronically inflammatory disease of the airways. At a cellular level, mast cells, eosinophils and T lymphocytes in particular play a role. In predisposed individuals, this chronic inflammation causes recurrent episodes of respiratory symptoms normally associated with airway constriction such as wheezing, shortness of breath, tightness in the chest and coughing, particularly at night and/or in the early morning. The latter are at least partially spontaneous or reversible with treatment. Due to the chronic inflammation, the airways are more likely to react to variable stimuli. [1–3]
Atopy	according to EAACI/WAO: individual and/or inherited tendency toward sensitization **(genetic predisposition)** due to which the body responds to contact with a low dose of normally occurring environmental allergens with the production of IgE antibodies **(IgE-mediated sensitization)**. Typical symptoms such as asthma, rhinoconjunctivitis or eczema may result. Normally, at this concentration, no persistent IgE response would result. Atopy is therefore the clinical manifestation of an elevated IgE response rate. It cannot be diagnosed in the absence of documented IgE sensitization (e.g. in the serum or via the skin prick test). However, as neither a positive skin prick test nor the presence of IgE antibodies per se can be considered indicators of an atopic constitution, IgE-mediated asthma should not be referred to generally as atopic asthma. [1–3]
Hypersensitivity	according to EAACI/WAO: causes objectively reproducible symptoms or signs of hypersensitivity in predisposed patients, which occur in response to exposure to a defined stimulus that is easily tolerated by a healthy patient. [1–3]
Incidence	number of individuals who newly develop a single disease within a certain period of time (typically one year). [6]
Non-allergic asthma	according to EAACI/WAO: the preferred term for **"non-immunologically contingent asthma"**. It is recommended that the old terms "extrinsic/intrinsic" and "exogenous/endogenous" no longer be used to differentiate between the allergic and non-allergic subgroups of asthma. [1–3]
Prevalence	percentage of the population that suffers from a disease. **Cumulative prevalence** refers to the total number of individuals who have suffered from this disease at any one point in time. **Point prevalence** describes the number of individuals suffering from this disease at a specific point in time. [6]
Rhinoconjunctivitis	allergic mediated disease at the nasal mucosa (rhinitis) and the eyes (conjunctivitis), which occurs after allergen exposure by an IgE-mediated hypersensitivity reaction should be referred to as "**allergic rhinoconjunctivitis**". Most cases are IgE-mediated. Depending on the duration of the symptoms, it may make sense even in this case to distinguish between "**intermittent**" and "**persistent**" **allergic rhinoconjunctivitis**. [1–3]

PATHO-PHYSIOLOGY



Scanning electron microscope picture of a pollen grain

CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

1906: The word "allergy" (allos = other, strange, peculiar; ergon = work, reaction) was coined by the Viennese pediatrician Clemens von Pirquet in a short essay for the Munich weekly magazine to describe an exaggerated reaction of the immune system [4]. Today, the term is defined as an immunologically mediated and allergen-specific hypersensitivity [5].

Traditionally, allergies have been divided into four types following a model developed by Coombs & Gell [6] in 1963. Since then, our understanding has expanded considerably. For this reason, EAACI and WAO suggest a new structure for differentiating between hypersensitivity reactions, based on the reaction that triggers the immunological mechanism [1]. Both systems are described below.

a) Classification according to Coombs & Gell: Division of hypersensitivity into four hypersensitivity reactions. The four types of hypersensitivity (tab. 1), of which Types I - III are antibody-mediated and result in a humoral response while Type IV is cell-mediated [7], can no longer be clinically distinguished from one another [7, 8].

Type I hypersensitivity reactions are often understood as "classic allergies". With Type I, the allergic reaction arises due to the production of specific immunoglobulin (Ig) class E antibodies against an antigen which is, in and of itself, harmless (= **allergens**). Many allergens that trigger a Type I reaction are low molecular, highly soluble proteins and components of larger complexes, such as animal hair or tree pollen. They enter the body through the mucous membranes of the airways and digestive tract [8, 9]. Upon contact with the allergen, the body normally produces IgM, IgG or IgA antibodies which dispose of the allergen without triggering symptoms. However, the IgE production leads to atopic reactions which manifest either locally or systemically (affecting the entire body) and can result in anything from itching, through respiratory difficulties, to shock and even death [9]. The immune response of hypersensitivity Type I follows very quickly after contact with the allergen, generally between a few seconds to 30 minutes (**immediate type**) [9]. Allergic rhinitis and conjunctivitis, allergic asthma, acute urticaria and IgE-mediated anaphylaxis belong to this type [8, 9].

With **Type II** hypersensitivity reactions, the response is humoral. The antibody-mediated destruction of the cells is carried out by complement-mediated cytolysis, antibody-dependent cell-mediated cytotoxicity or phagocytosis [8]. Examples include blood group incompatibility [10], rejection reactions follow organ transplants [11], autoimmune hemolytic anemia, Goodpasture syndrome [9], drug-induced cytopenia and autoimmune-mediated chronic urticaria [8].

Systematic of allergies acc. to Coombs and Gell

Tab. 1: Classification of hypersensitivity reactions based on the scheme by Coombs and Gell (based on [6, 10, 12-14])

	Additional names (selected)	Response time	Trigger
Type I	Immediate-type allergy (IgE-mediated); anaphylactic type; atopy	Immediate (< 1-30 min)	Pollen, animal dander, house dust mites, mold spores, insect venom, foods
Type II	Cytotoxic type; antibody-mediated cytotoxic hypersensitivity reaction	Minutes	Cell-associated antigens
Type III	Immune complex reaction; Arthus reaction	4-6 hours	Mold spores or particulate (e.g. from bird feathers or dung)
Type IV	Delayed type / late reaction (T cell-mediated)	24-72 hours	Nickel, household chemicals, skin care products, medications

In **Type III** hypersensitivity reactions, antigen-antibody complexes are formed in vessels and tissues and through these, complement, mast cell and other leukocytes are activated [8]. Type III allergies include exogenous allergic alveolitis (Birdkeeper's Lung, Farmer's Lung) and the drug-induced immune complex vasculitis [8].

Type IV hypersensitivity reactions arise through the activation of antigen-specific effector T cells, usually CD4+, which produce interferon-γ and other cytokines in order to stimulate macrophages (hyperactivation) [9]. Through initial contact with an allergen, the naïve T cells are sensitized to memory T cells, which are then activated through repeated exposure [8]. Due to the cellular mechanism, Type IV reactions require more time to develop. Contact allergies and drug eruptions belong to this type [8].

b) Classification according to WAO & EAACI: Differentiation of hypersensitivity according to immunological mechanism. In predisposed patients, **hypersensitivity** causes objectively reproducible symptoms or signs of hypersensitivity which present themselves in response to exposure to a defined stimulus that is easily tolerated by a healthy patient [1-3]. A distinction can be made between "**nonallergic hypersensitivity**", which is not caused by an underlying immunological mechanism and which manifests itself and "**allergic hypersensitivity**". The latter is triggered by immunological mechanisms. It may be antibody- or cell-mediated, though IgE antibodies are involved in most cases (**IgE-mediated allergies**). Accordingly, a distinction must be made with regard to "**non-IgE-mediated allergic reactions**" such as allergic contact eczema (T cell-mediated) or allergic alveolitis (IgM-mediated). IgE-mediated allergies, on the other hand, differ from one another according to whether **atopy** is present or not, such as in reactions to insect bites, helminths or drugs. An atopy can only be diagnosed based on evidence of IgE-mediated sensitization (e.g. in the serum or through a skin prick test) [1-3]. Fig. 1 shows a simplified hypersensitivity classification of the EAACI based on the immunological mechanisms.

Systematic of allergies acc. to EAACI

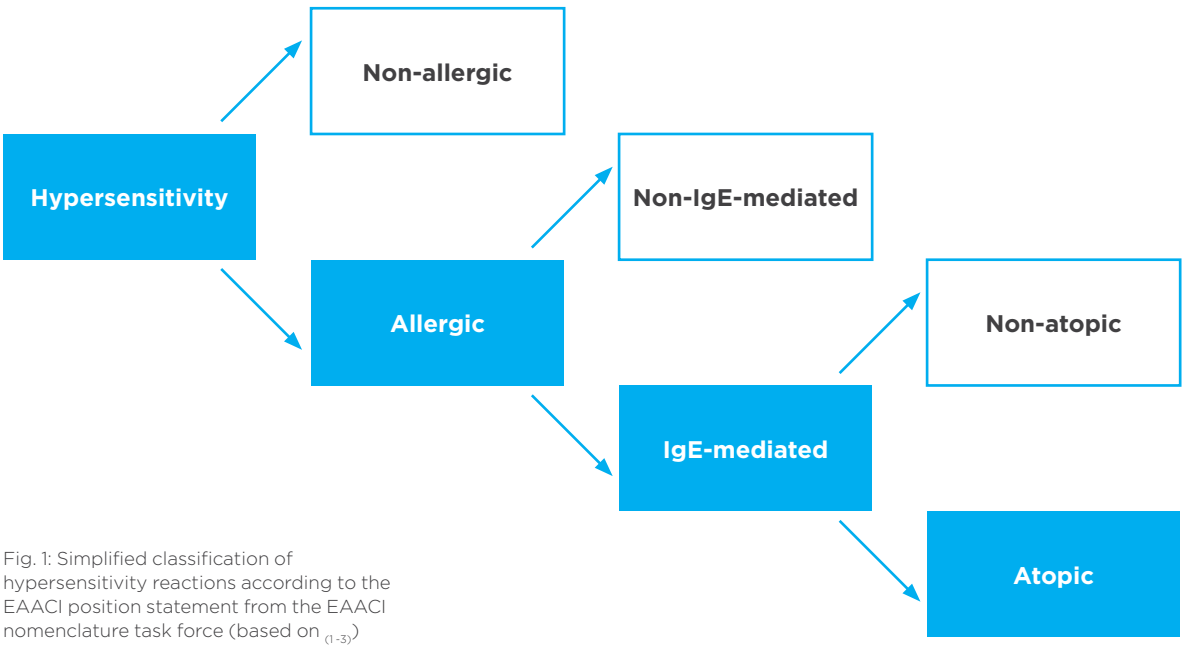


Fig. 1: Simplified classification of hypersensitivity reactions according to the EAACI position statement from the EAACI nomenclature task force (based on [1-3])

This brochure only describes allergic, IgE-mediated atopic hypersensitivities / Type I allergies, which are the most common forms of antibody-mediated hypersensitivity [7, 15]. These are divided into rhinitis, conjunctivitis, asthma, anaphylaxis, acute urticaria and angioedema.

DEVELOPMENT

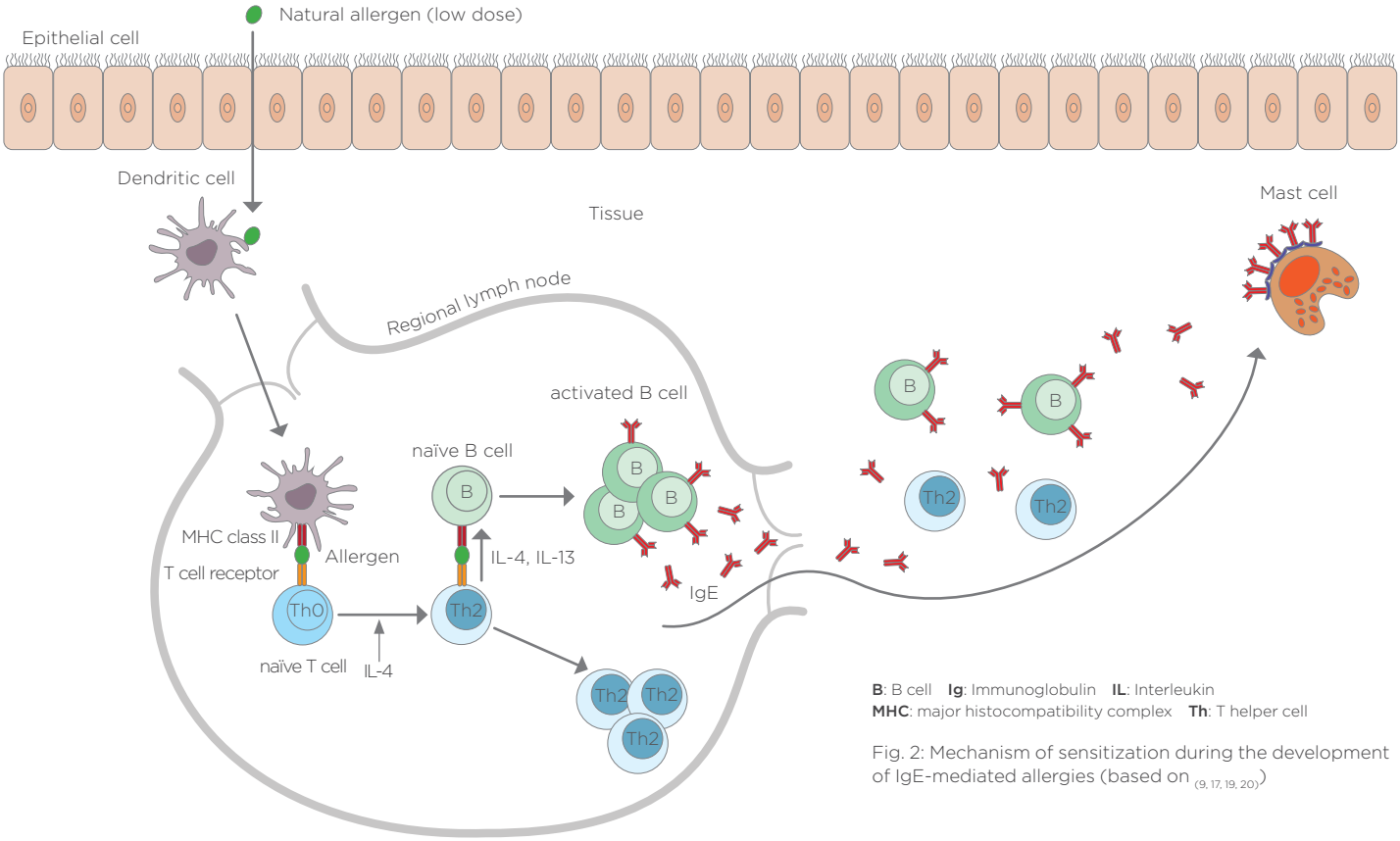
PATHOMECHANISMS

IgE-mediated allergic reactions take place in 2 main stages: sensitization (primary immune response) and the effector phase (secondary immune response). The latter is divided into an early reaction and a delayed reaction [8, 9, 16]*. The development of an IgE-mediated allergic reaction at the cellular level will be described in the following.*

Sensitization

If an allergen succeeds in entering the body through the respiratory passages or mucous membranes, it is taken up by immature dendritic cells and brought into the local lymph nodes. The dendritic cells mature, whereby they present peptides from the processed antigen to the major histocompatibility complex class II (MHC class II) on their cell surface. This complex is recognized by naïve T cells via their T cell receptor. Building on the MHC II recognition, IL-4 supports the differentiation of the T cell into a type 2 T helper cell (Th2) which produces large amounts of the cytokines IL-4 and IL-13. In the presence of these cytokines, naïve B cells undergo immunoglobulin class switch resulting in memory B cells which produces IgE antibodies. Both, Th2 and memory B cells clonally expand, exit the lymph node and make their way to the respiratory passages or mucous membranes. In the local tissue the IgE binds either directly to the allergen or to the high-affinity Fcε receptor (FcεR) on the surface of mast cells and basophils, which are then sensitized. The free IgE moves through the lymphatic vessels into the blood stream, which allows it to reach tissue further away. If it encounters basophils or mast cells on its journey, it sensitizes them as well by binding its Fc region to their FcεR molecule on their cellular surface. At this stage, patients do not show clinical symptoms of an allergic disease. [9, 17–20] Fig. 2 illustrates this phase at the cellular level.

Mechanism of allergic sensitization



B: B cell **Ig**: Immunoglobulin **IL**: Interleukin
MHC: major histocompatibility complex **Th**: T helper cell

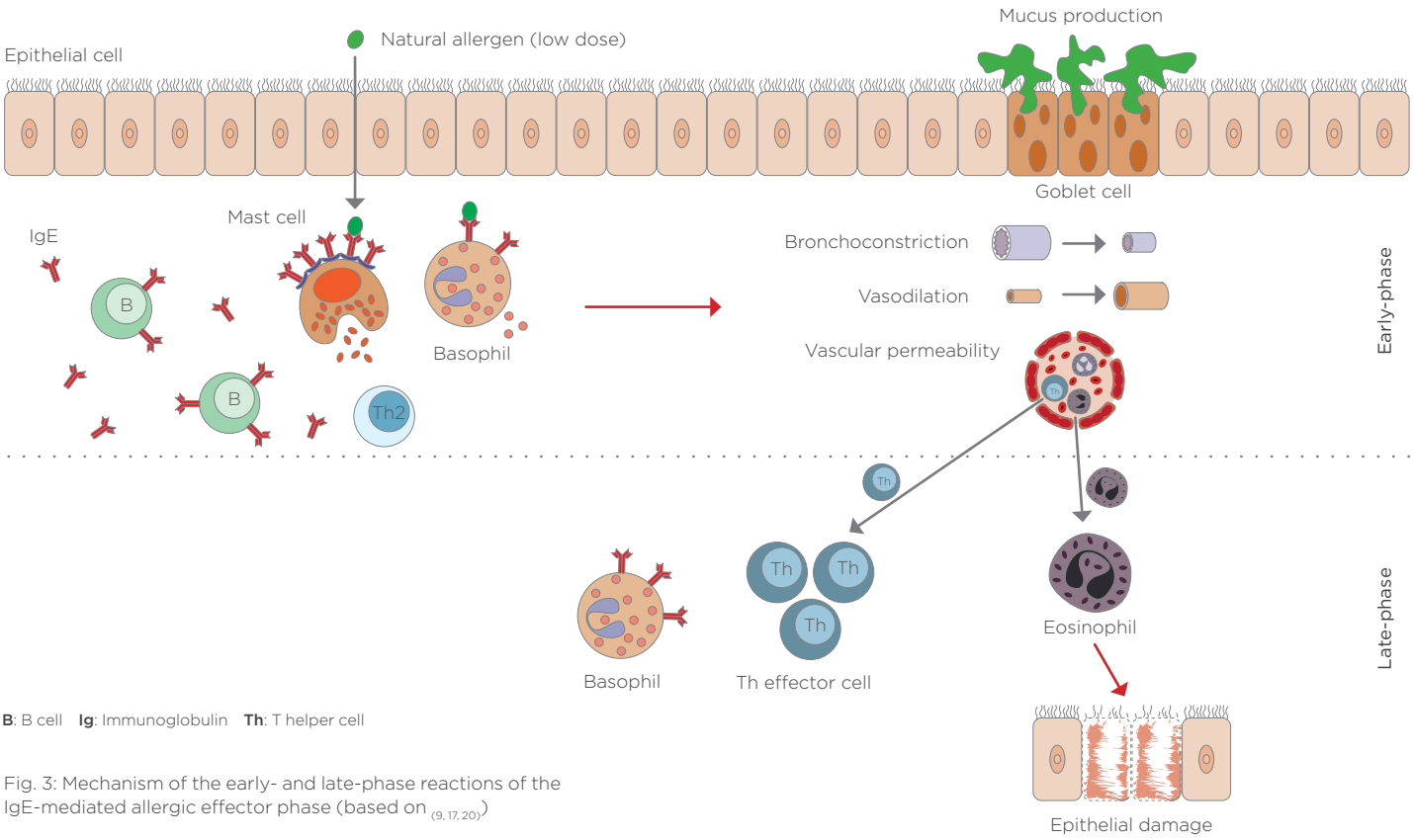
Fig. 2: Mechanism of sensitization during the development of IgE-mediated allergies (based on [9, 17, 19, 20])

Effector phase / symptomatic reaction

Early-phase reaction

If an allergen now enters a tissue containing mast cells that have already been sensitized and loaded with IgE, the allergen is immediately captured via the free antigen binding site of the IgE molecule on the mast cells. When several IgE molecules are engaged by allergens, the receptors are cross-linked, at which point the degranulation of the mast cell occurs. Mediators such as histamine, tryptases, cytokines (e.g. IL-8, IL-13), chemokines and growth factors (e.g. tumor necrosis factor-α (TNF-α)), leukotrienes, and thrombocyte activation factors (platelet-activating factor) are released. Additional mediators are generated through the enzymatic digestion of the mast cell membrane. Depending on the location of the tissue, these molecules trigger the typical tissue-specific symptoms of an allergic response [9, 17]. The inflammatory mediators induce expansion of blood vessels (vasodilation) and increase blood flow to the local tissue. Simultaneously, they induce an increased vessel permeability that cell and plasma proteins leak out of the vessel in the surrounding tissue. Vasoactive mediators induce dilatation of blood vessel resulting in a congestion of the upper airways. The interaction of the mediators with sensory nerve endings trigger itching and sneezing. Furthermore, the characteristic allergic symptoms arise: e.g. itchy, runny nose, watery red eyes, bronchoconstriction, redness of the skin and coughing [21]. These symptoms are triggered by the cascade activated by the mast cells which are normally involved in fighting parasites: all of the symptoms were designed to flush parasites out of the body. However, following sensitization the symptoms now occur after contact with harmless allergens and are typical for the allergic immediate reaction. [9, 17, 20, 21] Fig. 3 illustrates this phase at the cellular level.

Mechanism of the allergic early- and late-phase reaction



B: B cell **Ig**: Immunoglobulin **Th**: T helper cell

Fig. 3: Mechanism of the early- and late-phase reactions of the IgE-mediated allergic effector phase (based on [9, 17, 20])

Late-phase reaction

This phase begins around 4-6 hours after the initiation of the early-phase reaction and often peaks after 6 to 9 hours. However, it does not occur in every allergic patient and sometimes starts immediately after the early-phase reaction [17]. The chemotactic factors secreted during the immediate reaction induce the migration of leukocytes out of the blood vessels into the allergen rich tissue. Th2 effector cells, activated mast cells and basophils secrete cytokines like IL-4, IL-5, IL-9 and IL-13 which particularly attracts and activates eosinophils. These cytokine also play a key role in the maintenance of allergen-specific IgE levels, activation of eosinophils, recruitment of inflammatory cells to inflamed tissues, production of mucus and tissue inflammation and damage [19]. The epithelial cells of the airways appear to be highly sensitive to some destructive molecules. In fact, the clinical symptoms of asthma can be traced back to the characteristics of the activated eosinophils. [9] Eosinophils release basic proteins that damage epithelial cells. Further release of inflammatory mediators (e.g. IL-13, TNF-α) increases mucus production in the goblet cells [17, 22] and, in allergic asthma, a narrowing of the bronchi and bronchial hyperreactivity [17]. T cells may contribute to vasodilation [17]. Fig. 3 illustrates this phase at the cellular level.

RISK FACTORS FOR DEVELOPING ALLERGIES

Apart from genetics, environmental influences also play a role in the development of allergic diseases.

Endogenous factors

- **Genetic:** There is a genetic predisposition for developing allergic diseases [5, 23–25]
- **Age/Gender:** During childhood, boys are more often affected than girls, though in adults, women are affected significantly more often [26]
- **Comorbidities:** There has been an increase in atopic diseases. Children with eczema often subsequently develop asthma and then allergic rhinoconjunctivitis, the "atopic march" [27].

Exogenous factors

- **Climate:** Climatic changes can also increase the risk of allergic reactions [23]
- **Allergen concentration:** A strong presence of allergens in the environment also seems to have an influence on asthma and rhinitis [23]
- **Place of residence:** The prevalence of atopic diseases in urban areas and industrialized nations is higher than in the country or in developing countries [28]
- **Siblings:** Siblings reduce the risk of developing an allergy [29]
- **Air pollution:** Air pollution has also been suggested as an additional cause for the elevated prevalence in cities and industrialized nations [23]. Air pollutants such as ozone, nitrogen oxide and fine particulate can damage the mucous membranes of the airways and make it easier for allergens to enter the body
- **Smoking:** Even tobacco smoke appears to be implicated as a cause for allergic diseases [30]
- **Socio-economy:** Higher socio-economic status also increases the frequency of disease [26]
- **Drugs:** The intake of paracetamol by the mother during pregnancy [31] and by the child during its first years of life [32] seems to increase the risk for developing asthma.

Hygiene hypothesis and farm effect to explain the development of allergies

Hygiene hypothesis: postulated in 1989 by Strachan [33]; improvements in hygiene have resulted in decreased exposure to microbial components in early life which leads to an imbalance of the immune system with a predisposition to the development of allergic diseases. This especially applies to the IgE-mediated response which is specialized in parasites. In the absence of real enemies, the immune system of an allergic subjects recast against harmless substances like tree or grass pollen, house dust mites or food to remove them from the body.

Farm effect: early childhood exposure to farms protects from allergic rhinitis even in the long-life [23, 26, 33–38].

The allergic immune response in IgE-mediated atopic allergies is induced by a high concentration of Th2 cells, which manifests as increased IgE production. In binding to allergen-specific IgE, mast cells release the mediators of the immediate allergic reaction. Cytokines, also secreted by activated Th2 cells, further the immigration and activation of eosinophils, the persistence of which in the tissue leads to a chronic "allergic inflammation". The late phase reaction is characterized by an eosinophil-related inflammation and bronchial hyperreactivity. Several endogenous and exogeneous factors favor the development of allergies. The changing lifestyle with increasing hygiene and strong environment pollution is an additional risk factor.

CLINICAL MANIFESTATIONS

Aeroallergen induced IgE-mediated allergies cause symptoms at the nose (allergic rhinitis), the eyes (allergic conjunctivitis), the upper airways (allergic asthma) and the skin (urticaria, angioedema). An anaphylaxis is the maximal variant of an allergic early-phase reaction which is the most frequently life-threatening emergency in the allergology. Moreover, IgE-mediated allergies may cause symptoms in the gastrointestinal tract, in the ears and more seldom at other organs which are not further described in the following. [39]

ALLERGIC RHINITIS

Synonyms: Rhinitis allergica, allergic sniffles, hay sniffles, hay fever, pollinosis.

This is an inflammation of the nasal mucous membranes, which arises due to exposure to an allergen and an IgE-mediated sensitization and demonstrates at least two of the following symptoms: rhinorrhea, obstruction of the airways with obstruction of nasal breathing, sneezing or itching [38, 40, 41]. All symptoms may resolve spontaneously or following medical treatment [41, 42]. Allergic rhinitis can also be accompanied by various comorbidities including conjunctivitis [2, 43, 44], asthma and/or sinusitis [44].

Tab. 2: ARIA classification of allergic rhinitis

Duration of symptoms	
Intermittent symptoms	**Persistent symptoms**
▪ Less than 4 days per week ▪ OR less than 4 consecutive weeks	▪ 4 or more days per week ▪ AND 4 or more consecutive weeks

Strength of symptoms	
Mild	**Moderate-severe**
▪ Normal sleep ▪ Normal daily activities, sport, leisure ▪ Normal work and school ▪ No troublesome symptoms	▪ Sleep disturbance ▪ Impairment of daily activities, sport, leisure ▪ Problems caused at school or work ▪ Troublesome symptoms

Tab. 2: Classification of allergic rhinitis according to ARIA (Allergic Rhinitis and its Impact on Asthma). Each box may be further subclassified into seasonal or perennial (based on [41, 56])

Frequent sensitizations to aeroallergens in Europe

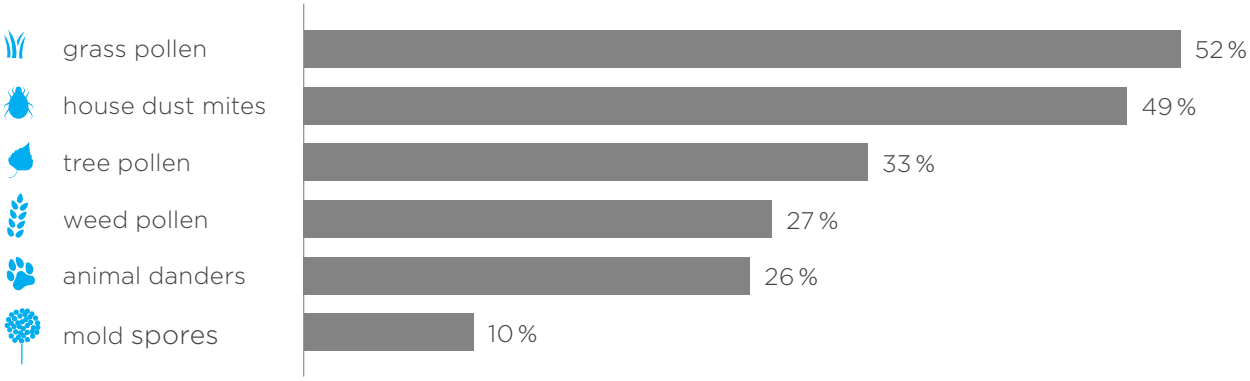


Fig. 4: Percentage of patients in Europe with a clinical diagnosis of allergic rhinitis showing specific IgE to the most common aeroallergens (based on [57])

At the beginning of the 19th century, allergic rhinitis was seen as highly unusual [38, 45], though with increasing industrialization it began to spread in western countries [46]. Its development appears to be influenced by genetic and environmentally determined factors [38, 47]. At the same time, allergic rhinitis represents a global health problem which cuts across all ethnic groups and has a negative impact on sleep, performance at school or work, social life and quality of life [38, 41]. Patients with allergic rhinitis are also three times as likely to develop asthma [48]. There are even hints, that allergic rhinitis is often associated with mood disorders such as phobias and depression, and also suicidal acts [49, 50] - this begins in childhood [51] because the neuroimmunological and pathophysiological processes set in motion during an allergic response influence neuronal functions in the brain [50]. For this reason, allergic rhinitis is a disease to be taken seriously. This is particularly important in view of the fact that this is the most common allergy worldwide [52] and one of the most common diseases overall [53].

Previously, allergic rhinitis was divided into seasonal, permanent and occupationally dependent, according to the exposure period [54]. This classification, however, is unsatisfactory because, for example, many patients have multiple sensitivities [55]. Non-allergic factors can also contribute to nasal symptoms [41]. It has therefore been suggested that a distinction should be drawn between **intermittent allergic rhinitis** (**IAR**; symptoms on fewer than 4 days per week or in fewer than 4 consecutive weeks per year) and **persistent allergic rhinitis** (**PAR**; on more than 4 days per week and in more than 4 consecutive weeks per year). The severity of the symptoms of allergic rhinitis can be classified as “mild” or “moderate - severe” (tab. 2) [41, 56].

The allergens that more frequently trigger allergic rhinitis are pollen, mites, mold, animal hair and insect body parts, such as those of cockroaches. Fig. 4 shows the allergens to which patients in Europe with allergic rhinitis are most commonly sensitized [57]. Depending on the presence of the allergens, the appearance of symptoms can be seasonal (pollen allergy) or year-round (mite, animal and mold allergy) [21]. The types of pollen responsible for rhinitis symptoms vary widely with local, climate, and introduced plantings [58]. Patients with pollen allergies often suffer from an itchy, runny rose with bouts of sneezing, while those allergic to mites have primarily reported a blocked nose with serous hypersecretion when getting out of bed [21].

ALLERGIC CONJUNCTIVITIS

Synonyms: Conjunctivitis allergica, allergic inflammation of the conjunctiva

Symptoms which point to allergic conjunctivitis following exposure to an allergen and sensitization are pruritus, hyperemia, itching and increased lacrimation of the eyes. The symptoms appear in both eyes and normally accompany rhinitis [40, 43]. General photophobia should be ruled out. In cases of more significant allergen exposure, acute bulbar edemas in the conjunctiva may be present [43]. A distinction is drawn between seasonal and perennial allergic conjunctivitis. Additional allergic conjunctival diseases that must be distinguished from allergic conjunctivitis are atopic keratoconjunctivitis (present in conjunction with atopic dermatitis), vernal keratoconjunctivitis ("spring catarrh") and giant papillary conjunctivitis (the latter two are accompanied by conjunctival proliferation) [43].

Allergic conjunctivitis arises from exposure to an allergen that triggers an IgE-mediated mast cell activation through the 2 phase immunopathogenesis described above, which sets an inflammation cascade in motion [41, 59]. Lymphocytes and eosinophils also play a major role [43].

Allergic conjunctivitis appears to be twice as prevalent among women than men [43]. In 65-70 % of cases, allergic conjunctivitis is accompanied by allergic rhinitis [43] and the diseases is therefore referred to as allergic rhinoconjunctivitis [2].

ALLERGIC ASTHMA

The word "asthma" is based on the Latin asthma and the Greek ásthma (ἄσθμα), meaning "difficult breathing, anxiety" [60] and describes one of the main symptoms.

Asthma is a life-long, chronic inflammatory disease of the respiratory passages which rises from an interaction between various cells and their components. It often begins in childhood and is connected with bronchial hyperreactivity, which leads to recurring attacks characterized by wheezing, coughing, shortness of breath and tightness in the chest, though the symptoms are particularly pronounced at night and in the early morning. Due to a narrowing of the airways, these attacks are accompanied by obstructed breathing and are often reversible, either spontaneously or with treatment. However, if they remain untreated they can lead to death. Furthermore, in the course of the disease, progressive and irreversible changes to the structure of the airways may occur ("remodeling"). [61–64]

A strong genetic component exists for developing allergic asthma, particularly as a child. Usually, there is already an atopic disease present in childhood, such as atopic dermatitis or allergic rhinitis, and the asthma develops additionally ("atopic march"). Allergic rhinitis is also a precursor in adults. Apart from allergens, asthma can be triggered by a variety of other factors such as cigarette smoke, air pollution, severe obesity, food, viruses, sports or stress. [5, 62, 64]

It is anticipated that in the year 2025, 400 million individuals will suffer from asthma globally. The influence of this disease on a patient's quality of life is extremely high, as are the resulting costs. [61, 65]

Due to the reversibility of the narrowing of the airways, a diagnosis is very difficult. Pulmonary function tests demonstrate an obstructive impairment of respiration with increased airway resistance and reduced one second capacity (FEV1).

ALLERGIC ANAPHYLAXIS

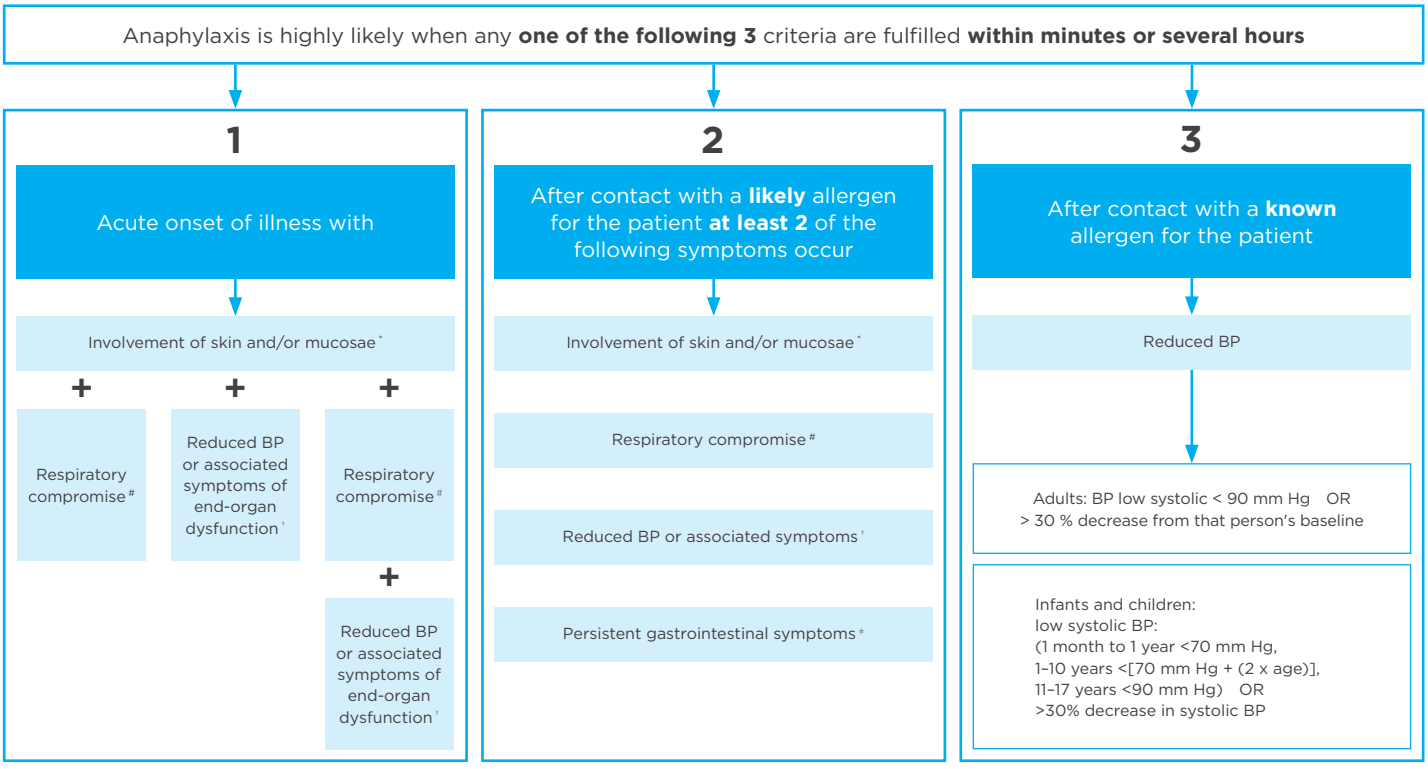
The first written description of anaphylaxis can be found in 1902 in the works by von Portier [66].

Anaphylaxis refers to an life-threatening, acute, severe systemic reaction with symptoms of an immediate allergic reaction which affect the entire body and require immediate medical intervention [2, 67, 68].

Allergic anaphylaxis is generally caused by an immune mechanism. It generally occurs following contact with an allergen in individuals who have been correspondingly IgE-sensitized, triggered by the sudden release of vasoactive mediators by active mast cells and basophils. The anaphylactic reaction triggered by the IgE antibodies can be referred to as IgE-mediated allergic anaphylaxis. However, it can also trigger a similar, complement-dependent pathology through specific antibodies of other classes via the building of circulating immune complexes (immune complex anaphylaxis). There are also numerous anaphylactic reactions for which no immunological sensitization can be documented. Previously, these were referred to as "pseudoallergic" reactions, though now they are termed "non-allergic anaphylaxis". The use of the expression "anaphylactoid" reaction should be avoided. [2, 67, 69–75]

The symptoms of anaphylactic reactions are wide-ranging, involving at least two organ systems at the skin/mucosae, gastrointestinal or respiratory tract or cardiovascular system (fig. 5), begin as acute and can then progress very quickly. In most cases cutaneous symptoms occur but anaphylaxis can also develop in the absence of them. Moreover, nausea or vomiting may be associated with anaphylaxis. [68, 75] Following immediate successful treatment, the patient may experience occasional recurrence of the symptoms (biphasic anaphylaxis). For this reason, medical monitoring should be provided until safe, permanent remission of the anaphylaxis can be ensured. [76]

Anaphylaxis - clinical criteria



* e.g. generalized urticaria, pruritus or flushing, swollen lips-tongue-uvula
\# e.g. dyspnea, wheezing, bronchospasm, stridor, reduced peak exploratory flow, hypoxemia
† e.g. hypotonia (collapse), syncope, incontinence
ǂ e.g. crampy abdominal pain, vomiting

Fig. 5: Clinical criteria for diagnosing anaphylaxis (based on [68, 75])

BP: blood pressure

There have been few studies regarding the prevalence or incidence of anaphylactic reactions. On the one hand, this is due to the inconsistent use of the definition [73, 75], but on the other hand also because of the large selection of ICD-10 codes that include anaphylaxis [73]. Epidemiological studies from the USA, Great Britain and Australia show incidence rates of 7 – 50 per year per 100,000 residents [77–79]. A 3-year Swiss study calculated an incidence rate of 7.9 to 9.6 cases per year per 100,000 residents following its examination of severely life-threatening anaphylaxis at the end of the 1990s [80]. This corresponds to the results of other studies [81, 82]. For Europe, it is estimated that 0.3 % of the population will experience anaphylaxis at some point during their lives [82]. In the meantime, the number of cases of allergic disease have increased. Retrospective studies suggest that for around 1% of all patients admitted to a clinic for emergency treatment, an anaphylactic reaction is the underlying cause [83]. Deaths due to anaphylaxis have been calculated in 2005 to be approx. 1-3 per year per million residents [3]. More recent data resulted in a range of 0.002 to 2.51 deaths per million person-years [84].

In childhood, anaphylactic reactions occur in boys more commonly than in girls. After puberty, the difference diminishes [85, 86].

There are several risk factors for the development of anaphylaxis, its severity and the resultant mortality. These include: age-related factors, concurrent illnesses (e.g. asthma and other chronic respiratory diseases, mastocytosis), simultaneous administration of medications (such as β-blockers or ACE-inhibitors) and cofactors (e.g. physical stress, fever, acute infection, premenstrual status, emotional stress). They are similar worldwide [67, 72]. However, the data show that bronchial asthma represents a very important risk factor [87]. Poorly managed asthma in particular is a risk factor for the severity of an anaphylactic reaction [73].

The molecule that triggers anaphylaxis generally enters the human body via oral or percutaneous/parental/hematogenous routes, though it is also possible that it was airborne and entered through the airways.

Among others, typical triggers include

- food
- insect venom
- drugs
- additives
- natural latex
- airborne allergens [67, 88].

If no trigger can be determined despite a detailed medical history and comprehensive examination, a diagnosis of idiopathic anaphylaxis is made [67].

Anaphylaxis is a medical emergency. Immediate identification and treatment is decisive [73]. Epinephrine (adrenaline) is the most important medication for the acute treatment of anaphylaxis. Most anaphylactic emergencies occur in the patient's private environment [73]. For such cases, there are emergency sets in which, in addition to the established epinephrine autoinjector, there are also an antihistamine, a corticosteroid and, for patients with asthma, a bronchodilator with metered-dose inhaler. Standardized anaphylaxis emergency plans help in using the individual medications [83]. The epinephrine autoinjectors are a great help in these situations because they can be applied so rapidly. Following an intramuscular injection in the thigh, the epinephrine is quickly absorbed and can save the life of the patient, if used immediately [67]. The standardized doses for autoinjectors of 0.15, 0.3 and 0.5 mg represent practical individual doses for this application. The EAACI task force gives the following recommendation for prescribing epinephrine autoinjectors for patients at risk for anaphylaxis:

- 0.15 mg for children from 7.5 kg to 25-30 kg,
- 0.3 mg for children from 25-30 kg,
- at least 0.3 mg for adolescents and adults [89].

Epinephrine is effective for all the symptoms during anaphylaxis. If they do not improve or worse the intramuscular epinephrine injection can be repeated after approx. five minutes [73, 89]. The scope of the therapy depends on the severity of the reaction [67, 73].

URTICARIA AND ANGIOEDEMA

A direct allergic reaction of the skin or the mucous membranes can manifest itself as urticaria (hives) or angioedema. In their most severe forms, these are components of anaphylaxis. (90)

Symptoms of urticaria include characteristic wheals caused by an edema of the upper layer of the skin, nearly always accompanied by redness of the skin, local itching and burning. Wheals and redness reactions appear suddenly and are temporary, in other words the skin returns to its normal appearance within 24 hours, though sometimes after as little as one hour. (91–93)

The same wheals can be observed when histamine or a clinically relevant allergen is brought into contact with the skin, which is the method employed during the skin test during allergy diagnostics. There are various forms of urticaria and in this instance, too, it is possible to distinguish between immunological and non-immunological pathologies. It is possible to classify hives based on its duration. Acute hives last for less than 6 weeks while chronic hives persist for longer than 6 weeks. (91)

Angioedema is defined as a swelling of the deep layers of the dermis and the subcutaneous tissue of the mucous membranes, though this is most often accompanied by pain rather than itchiness. It also characteristically subsides slowly, taking up to 72 hours. (91, 93)

The hospitalization rate for urticaria is around 6 % per year, though children up to 4 years old are particularly affected. The hospitalization rate for angioedema is 3 %. In this case, the majority of persons affected are individuals over 65 years of age. (79)

EPIDEMIOLOGY AND HEALTH ECONOMIC RELEVANCE

The prevalence of IgE-mediated allergic diseases is generally underestimated and the number of affected patients worldwide increases, especially in the industrial nations. The socioeconomic costs of allergies in the airways are significant only by the impairment of labor force. With disease progression the treatment becomes more difficult and the costs increase. (5, 94)

EPIDEMIOLOGY

Global prevalence

Worldwide, allergic diseases adversely affect the lives of some 20-30 % of the population. According to estimates by the WAO, the numbers in some regions may even reach 40 % (23, 64). On average, this corresponds to more than 2 billion people (95). Despite regional differences, the incidence and prevalence of asthma and rhinitis are increasing all over the world (23, 96). Based on the dramatic increase over the last 60 years, the prevalence will reach 4 billion people by 2050 (5).

Allergic rhinitis alone affects some 500 million individuals, of whom 200 million also simultaneously suffer from asthma (38). Allergic rhinitis and asthma must be considered systemic inflammatory diseases. They often occur together: More than 80 % of asthmatics also suffer from rhinitis symptoms and 10 to 40 % of those with rhinitis have asthma (38).

Prevalence in Europe & the Industrialized Nations

In Europe, the prevalence of allergic sensitization that can be proven through an allergen-specific IgE in the serum or via a skin test is often over 40 % (97). Similar data can be found in the USA (98), Australia and New Zealand, whereby local fluctuations generally exist within the country itself (97), particularly in the larger countries. Nowadays, allergies are the most common chronic illness in the European Union (EU) (99). Fig. 6 shows the official data on allergy prevalence in various European countries (100).

In Europe, around 20 % of the population suffers from allergic rhinitis and an estimated 5-12 % have asthma (100). For children aged 6-7, the prevalence of allergic rhinitis is 8.5 %, and for adolescents aged 13-14 it is 14.6 % (101). Every 4th child suffers from at least one allergy (64). According to a Europe-wide study, the prevalence of clinically confirmed IgE-mediated allergic rhinitis is 21.5 % in Spain, 24.5 % in France, 26 % in the United Kingdom and 28.5 % in Belgium (57). Depending on the study, the prevalence in Germany is given as 13-24 % (57, 102). Europe-wide, this results in a prevalence of 23 % for allergic rhinitis (fig. 7) (57). Based on the EU, this means that nearly 120 million people are affected (103). Of these, women are generally more affected than men, and the young more frequently than older individuals (26).

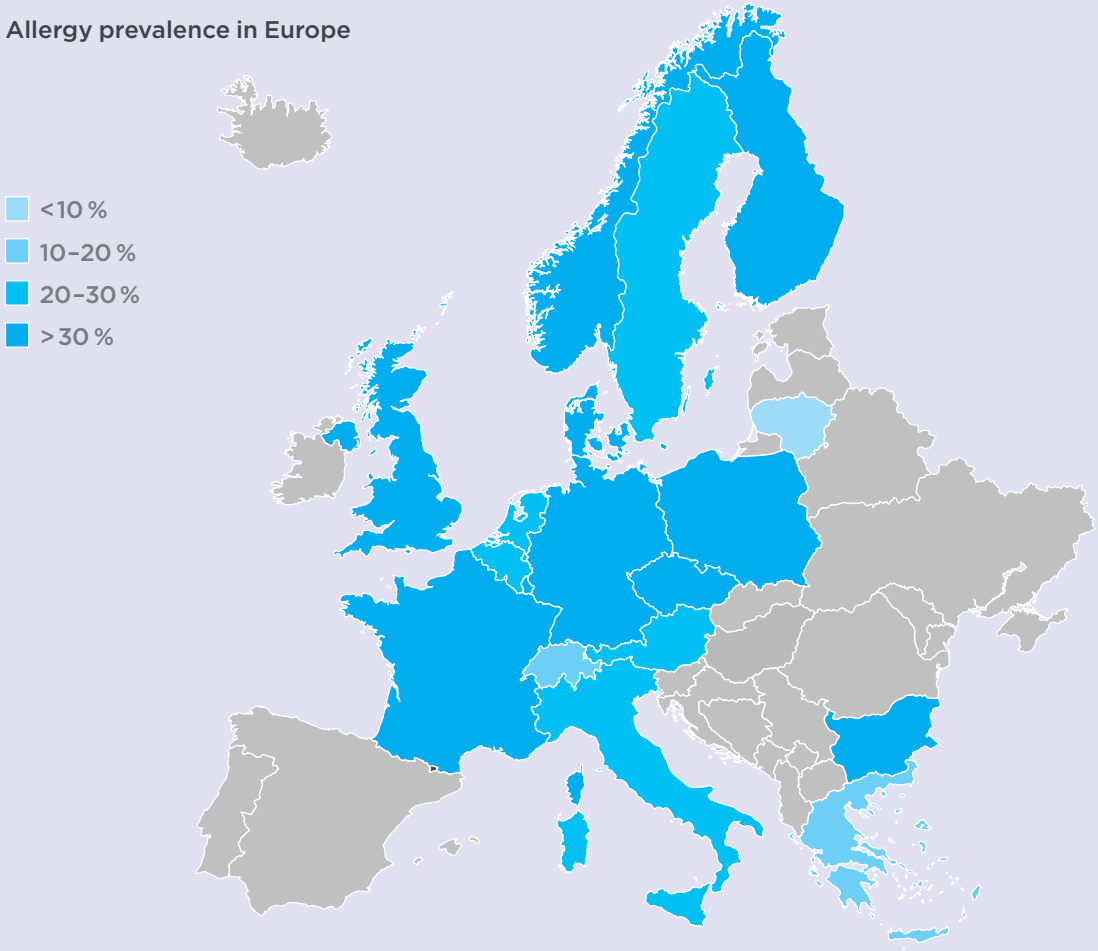


Fig. 6: Allergy prevalence (not only respiratory allergies) in different European countries (mod. acc. to [100])
(Reproduction with kind permission of EFA - European Federation of Allergy and Airways Diseases Patients' Associations)

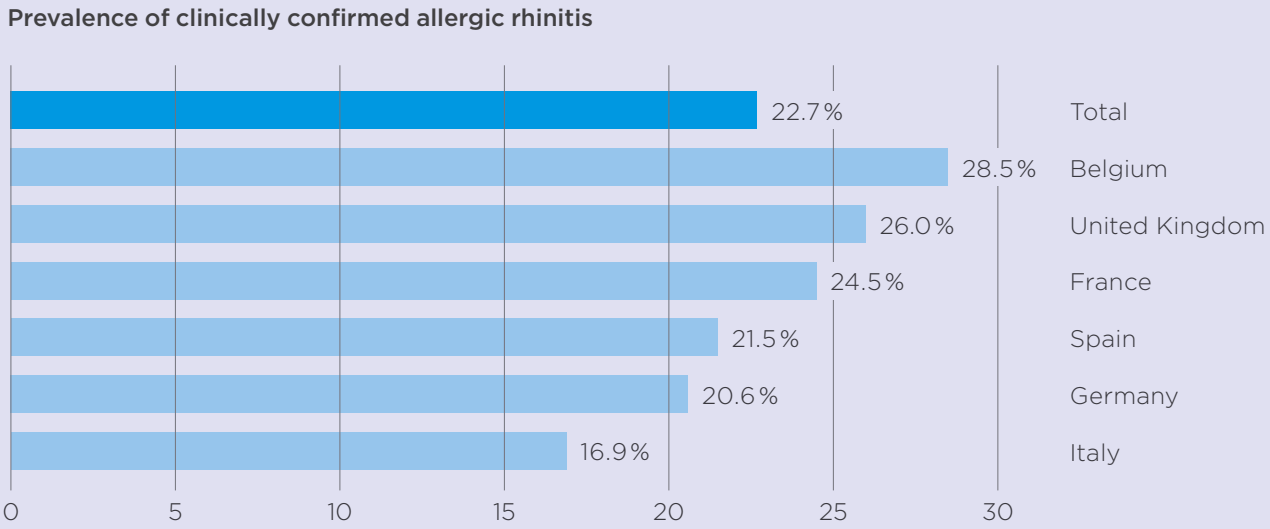


Fig. 7: Clinically confirmed prevalence of allergic rhinitis in different European countries, based on clinical studies, specific IgE measurements and disease-specific surveys (based on [57])

HEALTH ECONOMIC RELEVANCE

Despite their prevalence, their potential severity and their immense influence on quality of life, allergic diseases are trivialized in every segment of society [99, 104, 105]. Even patients do not take their disease seriously [99, 104], to the extent that many do not go to a doctor to receive a differentiated diagnosis and therapy, resulting in inadequate treatment.

In a study of allergic rhinitis, 50 % of allergy sufferers in five major EU countries were found to be receiving inadequate treatment [104]. Another publication assumes that 90 % of the EU employees who suffer from allergic diseases of the airways or the skin are receiving sub-optimal treatment [99]. The failure to take such allergies seriously intensifies personal suffering, as well as the risk of contracting a secondary disease, not to mention the socioeconomic costs.

Between December 2001 and September 2002, the average productivity loss per employee and year was investigated in the United States for different diseases. Allergic rhinitis was the most prevalent of the selected condition, causing costs 6-fold higher than for diabetes and even 10-fold higher than for coronary heart diseases. Diabetes and congestive heart failures are the focus of disease management programs, since they cause high costs because of their severe comorbidities. Although, highly prevalent diseases with comorbidities which are often trivialized cause high or even higher costs. [106]

Based on a model calculation, the annual costs of absenteeism and reduced concentration and productivity in the labor force within the EU could amount to between 55 and 150 billion Euro, depending on which prevalence and impairment is assumed. Treatment as per the guidelines, on the other hand, could yield savings of 50-140 billion Euro [99, 107].

Today, IgE-mediated allergic diseases are called “epidemic of the 21st century”. 20-30 % of the population worldwide are affected. Genetic and environmental factors play a major role in the development. Often allergies are trivialized resulting in an insufficient medical treatment. Nevertheless, allergies cause high socio- and health economic costs, especially by absenteeism and reduced concentration and productivity in the labor force.

DIAGNOSIS

Scanning electron microscope picture of a mite

The complete diagnosis of an IgE-mediated allergic reaction or disease begins with the medical history and a physical examination in order to create a preliminary diagnosis of a suspected allergic disease. To confirm this, sensitization tests are required, the most commonly used is the skin prick test. In cases without a clear indication, a supplementary provocation test, such as the nasal provocation test, is performed to clarify the clinical relevance. [108]

The schematic procedure in case of suspected IgE-mediated allergic rhinitis or rhinoconjunctivitis, especially concerning natural aeroallergens, is shown in fig. 8.

Diagnosis of allergic rhinitis/rhinoconjunctivitis

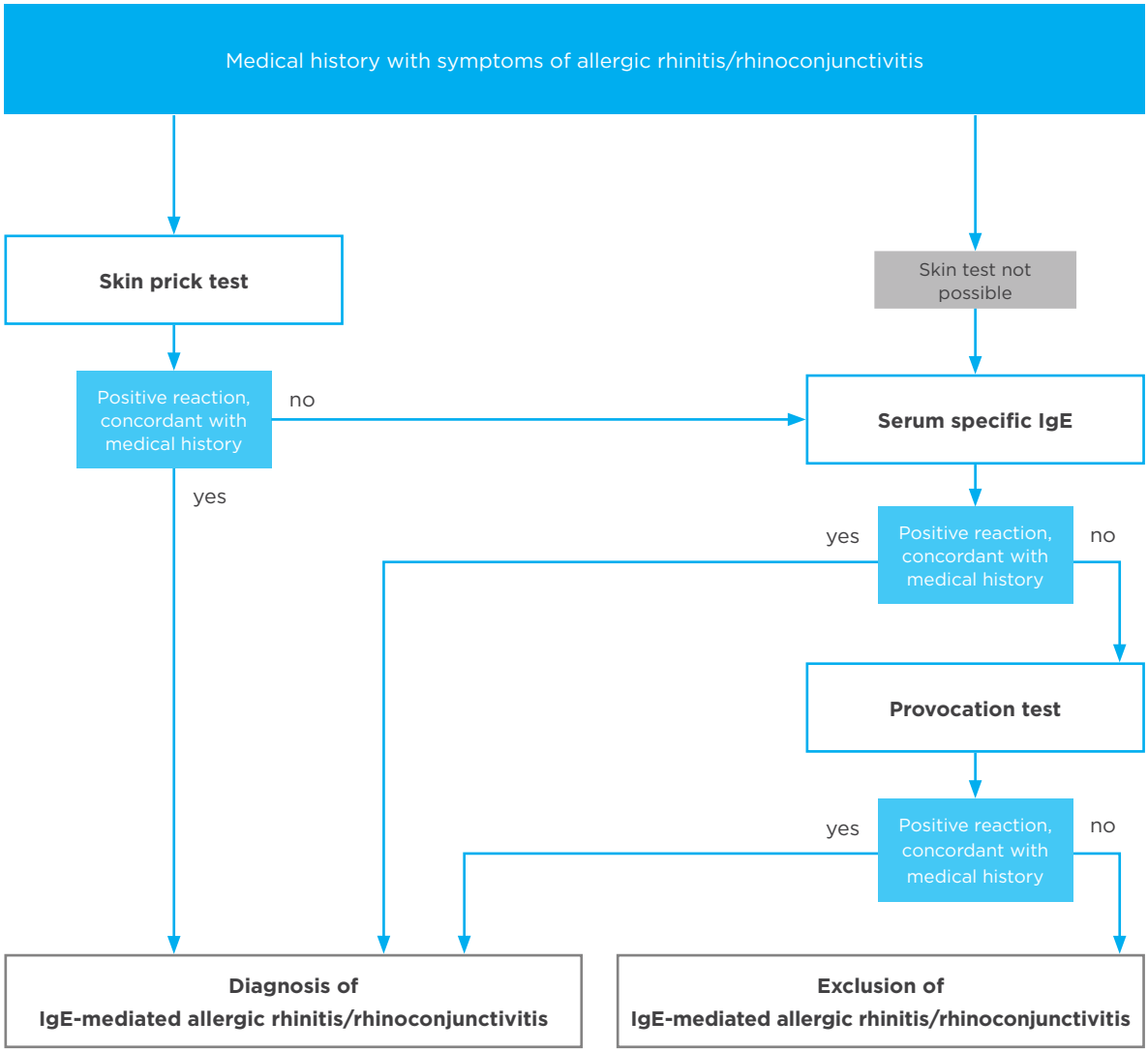


Fig. 8: Algorithm for evaluation of patients with suspected IgE-mediated allergic rhinitis and rhinoconjunctivitis (based on [109, 110])

MEDICAL HISTORY

A thorough medical history and a physical examination are of paramount importance in the diagnosis of allergic diseases [23, 111] and constitute the primary diagnostic tool [112].

Beside the typical physical examination nose, lung, eyes, ears, skin and the respiratory tract should be investigated as to the patients complaints [111]. Asking questions about the medical history allows conclusions with regard to the severity of the diseases, the probable degree of sensitization and possible allergens [11, 111]. A medical history questionnaire is recommended. Tab. 3 lists some relevant aspects for the medical history of allergic patients.

Medical history of allergic diseases

Tab. 3: Possible questions for medical history to patients with suspected IgE-mediated allergy (based on [11, 23, 111, 113–115])

A detailed medical history should include, among other things, the following parameters	
Symptoms	What symptoms are being experienced? What are the chief complaints? When did the complaints first occur? At what times of the year or day do the symptoms occur? Frequency, severity and duration of the symptoms? Occurrence / improvement / worsening of the symptoms in specific situations? (e.g. at home, in the workplace, on vacation, in the open air, during exposure to certain things, during contact with animals or foods, when undertaking certain activities, during menstruation, accompanied by certain feelings, odors, fumes) Are there any symptom-free intervals? When do these occur?
Family history	Does anyone in the patient's family suffer from allergies, respiratory or skin conditions?
Home / workplace	Size of the town or city, age of the house, carpets, air conditioning, detergents, other sources of specific allergens?
Cigarette smoke	Passive or active smoker, quantity?
Previous tests and treatments	What were the results of the tests performed to date? What treatments were initiated to date, and how beneficial were they?
Impact of the disease	Missed work days, social adjustment, nocturnal symptoms, frequency of unscheduled physician visits, visits to an emergency room or hospital stays, fatigue, interrupted sleep, difficulties with studying or concentration, quality of sexual life?
Psychosocial situation	Low self-esteem, shyness, depression, anxiety, hyperactivity?
With children [107]	Did mother smoke during pregnancy, type of birth, nutritional history?

Based on the outcome of the medical history and physical examination, potential allergens are screened in vivo through a skin test. [23, 109]

A detailed medical history is an essential component during allergy diagnosis. Narrowing down when and/or where allergic symptoms occur, provide the basis for the identification of relevant allergens and the potential therapeutic procedure.

SKIN TESTS (IN VIVO DIAGNOSTICS)

Allergen-specific IgE antibodies can be confirmed in the skin. Skin tests are considered the gold standard for confirming or excluding IgE-mediated sensitization and therefore constitute the foundation for the identification of specific allergy-inducing allergens. (23)

In patients with IgE-mediated allergic reactions, mast cells with specific IgE antibodies are present in the dermis. These must be brought into contact with the "matching" allergen in the skin to trigger a mast cell activation with subsequent release of mediators, especially histamine (88, 116). This results in a flare and wheal response which can be quantified. The resulting size of the wheal depends on various factors, such as the extent of the sensitization, the number of mast cells and the strength of the allergen extract (23). Several allergens can be tested simultaneously since the reaction to a specific allergen is limited to the respective area of testing (116).

Methods

- the skin prick test (SPT), a percutaneous test which is used most frequently because of its characteristics. ➔ See detailed description page 32.
- the intracutaneous or intradermal test (ICT) which is more sensitive but less specific, more painful and time-consuming than skin prick testing and involves a higher risk of systemic reactions (117,118).
- the scratch test (scarification test), which involves placing the test solution on a superficial, non-bleeding scratch. It is no longer used due to the difficulty of standardizing or reproducing it, the frequency of unspecific results or those which are difficult to interpret, the larger amount of mechanical irritation and the elevated risk of systemic reactions (38, 119).
- the rub test, during which a native material is rubbed with pressure on an area of approx. 5 x 5 cm on the volar forearm (120).
- the patch test, during which the test material is left on the skin for 24–48 hours for evidence of contact allergies (121). The patch test with immediate results is an ideal choice with natural allergens for which a severe reaction is anticipated (122). Here, the test material is left on the skin in an occlusive application for 20 minutes.
- The prick-to-prick test, during which the prick lancet is first pricked in the non-liquid substance (especially for fresh foods and vegetables) to be tested, and directly thereafter the skin of the patient to be tested (116).

Indications

- suspected IgE-mediated allergy based on the medical history and clinical symptoms (116).

Contraindications

- poor general condition (88)
- skin condition in the test area (88)
- instable or inadequately treated bronchial asthma (FEV1 < 70 % target value!) (88, 115)
- pregnancy (88, 116)
- treatment with β-blockers (or less often ACE-inhibitors) because of reduced response to epinephrine in case of systemic adverse events (88, 116).

Skin test not possible?

1. perform in vitro tests
2. skin test still necessary?
3. ➔ if applicable, hospitalize patient for stationary surveillance (88).

Avoid misinterpretations

- age: with persons over 65 and small children of less than 2 years, the reaction is often less pronounced [23, 123–125]
- concomitant medication may interfere with the result (washout periods see tab. 4) [23, 111]
- controls: employ positive and negative controls [5, 23]
- test area: only test on healthy skin; avoid sections of skin with eczema or other lesions [5, 111, 126]
- dermographism is the most common cause of false positive results [5, 23]
- neurological conditions or infectious diseases such as leprosy can cause false negative results [126]
- always compare test results with the patient's medical history and the physical examination, as a positive skin reaction does not always imply a clinically relevant allergy [23, 127]
- penetration depth of the lancet: not deep enough or too deep with subsequent bleeding can produce false negative or false positive results respectively [88].

Washout periods before skin testing

Tab. 4: Medications which interfere with the skin reactivity and have to be discontinued with a respective time interval (washout period), since they cause a false-negative SPT result

Medication	Recommended washout period before skin testing
α-sympathomimetics – nasal	
Oxymetazoline	None [128]
Atypical antidepressants / sedatives	
Mirtazapine, Quetiapine	5-7 days [129]
Bupropion, Eszopiclone, Trazodone	0-3 days [129]
Antihistamines – nasal	
Azelastine	0-2 days [130–133]
Levocabastine	0-3 days [131]
Antihistamines – eye drops	
Levocabastine	0-1 day [123, 128, 131]
Antihistaminines – oral	
Azelastine	7 days [131]
Cetirizine	3-5 days [129, 130]
Clemastine	3-10 days [123, 130, 134]
Dimetindene	7 days [130]
Ebastine	3-4 days [131, 135]
Fexofenadine	2-5 days [129, 136]
Hydroxyzine	2-8 days [137]
Loratadine/Desloratadine	2-7 days [129, 131]
Antihistaminines – sedatives	
Diphenhydramine	0-4.5 days [137]
Promethazine	1-4.5 days [137]
Benzodiazepines	
Clonazepam, Diazepam, Lorazepam, Midazolam	5-7 days [129]
β_2-sympathomimetics - inhaled	
Fenoterol, Reproterol, Salbutamol, Terbutaline	None [130]
β_2-sympathomimetics - oral	
Bambuterol	None [139]
Clenbuterol, Fenoterol, Salbutamol	None [130]
Terbutaline	None [130, 139, 140]
β_2-sympathomimetics - injective	
Reproterol, Salbutamol, Terbutaline, Theophylline (short to medium long acting, retard preparations)	None [130]

Medication	Recommended washout period before skin testing
Corticosteroids – nasal	
Beclomethasone dipropionate, Budesonide, Ciclenoside, Fluticasonpropionate, Fluticasonfuroate, Mometasonfuroate, Triamcinolone acetonide	None (128)
Corticosteroids – inhaled	
Beclomethasone, Fluticasone	None (116, 130)
Flunisolide	max. 1-2 days (130)
Corticosteroids – cutaneous[1]	
Betamethasone	3 days (141)
Corticosteroids – systemic	
Short term (up to 10 days) (< 50 mg/d Prednisolone equivalent)	> 3 days (116, 142)
Short term (up to 10 days) (> 50 mg/d prednisolone equivalent)	> 1 week (116, 143)
Long term (more than 10 days) (< 10 mg/d prednisolone equivalent)	None (116)
Long term (more than 10 days) (> 10 mg/d prednisolone equivalent)	> 3 weeks (116, 143)
H2-receptor antagonists[2]	
Famotidine, Ranitidine, Cimetidine	0-2 days (129)
Immunosuppressants	
Cyclosporin A	None (128, 144)
Leukotriene-receptor antagonists	
Montelukast	None (126, 145)
Mast cell stabilizers	
Sodium cromoglycate, cutaneous	None (146)
Ketotifen	At least 5 days (116)
Monoclonal antibodies	
Omalizumab[3]	6-7 months (147)
Proton pump inhibitors	
Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	None (129)
Serotonin norepinephrine reuptake inhibitor	
Duloxetine, Venlafaxine	None (129)
Selective serotonin reuptake inhibitor	
Citalopram, Paroxetine	None (129)
Escitalopram, Fluoxetine, Sertraline	None (129, 148)
Tricyclic antidepressants and tranquilizers	
Amitriptyline, Nortriptyline	5-7 days (129)
Doxepin	7 days (116, 149)

1 when used in the test area **2** especially if combined with another potentially antihistaminic medication **3** dose-dependent

The risk of a systemic reaction may increase in the event of

- severe anaphylactic symptoms in the patient's medical history (88)
- relevant complaints at the time of testing, especially asthma (117)
- polysensitized patients (153)
- testing with fresh foods or native allergens (153–155)
- allergen contact shortly before testing (88, 156)
- testing with highly concentrated allergens (122)
- elevated levels of baseline tryptase (116)
- intracutaneous testing (117)
- treatment with β-blockers (157).

While systemic reactions due to skin tests are very rare (117, 150–152), the provision of emergency care for an event such as this must nevertheless be guaranteed (88).

The washout periods listed here are often related to studies where medications are administered for short term. It is possible, if a patient is taking multiple drugs, that alone have a minor effect, the combination of these drugs could suppress the skin response. Therefore, a positive skin histamine response is an important prerequisite for performing skin testing with allergens (128).

There are no data available for combination preparations containing at least one of the active substances mentioned above.

Depending on the medical indication some medications listed above should not be discontinued without assistance from the prescribing provider (e.g. antidepressants, sedatives, corticosteroids). Otherwise, skin prick testing should not be performed.

Ideally, the allergist should discontinue medications for the minimal time necessary to produce accurate skin test results and avoid cessation of drugs that do not affect the testing (129).

This table makes no claim to completeness.

SKIN PRICK TEST

The skin prick test is used most frequently to selectively confirm or exclude in vivo a suspected sensitization to one or more specific allergen(s) [116, 126].

Advantages of the skin prick test compared with other skin tests

- easy to perform [5]
- immediate information about the sensitization [5, 116]
- higher specificity than intracutaneous tests [158]
- high correlation with clinical symptoms [38, 126, 159]
- good correlation with allergen-specific IgE (sIgE) in serum [160]
- good correlation with provocation tests [38, 161]
- systemic side effects are very unlikely for commercially available aeroallergens [126]
- safer than intracutaneous tests [126].

Test material and resources

Allergen extracts: National and international guidelines recommend to use test extracts that are immunochemically and biologically standardized, both qualitatively and quantitatively [123, 126, 162]. If these cannot be obtained, non-standardized commercially available extracts should be used instead [88].

Individual allergen extracts: If extracts for a certain allergen are not available, or if these have not provided usable results, and if the extract has a significant impact on the diagnosis or treatment, it can be prepared individually [88].

Controls: In order to be able to evaluate the patient's test reactions, it is absolutely essential, due to the diversity of skin reactions, that a positive and a negative control be tested at the same time [123, 126]. These should always originate from the same manufacturer as the allergen solution.

- Negative control: allergen-free solution [38, 116]; it should trigger a completely negative reaction. In rare cases, such as in the case of dermographism, patients also react to the negative control [38]. The prick lancet can also trigger a traumatic reaction. In these cases, a reliable interpretation is not possible [38].
- Positive control: e.g., histamine dihydrochloride solution (some manufacturers offer a 0.1% solution, others a 1%) is used to determine reduced skin test reactivity which may occur as a result of diseases or drug intake, differences in technical implementation by the medical personnel or with patients who display only a minor reaction to histamine [38].

Prick lancet: Metal lancets have displayed significantly higher reproducibility compared to plastic ones [163, 164].

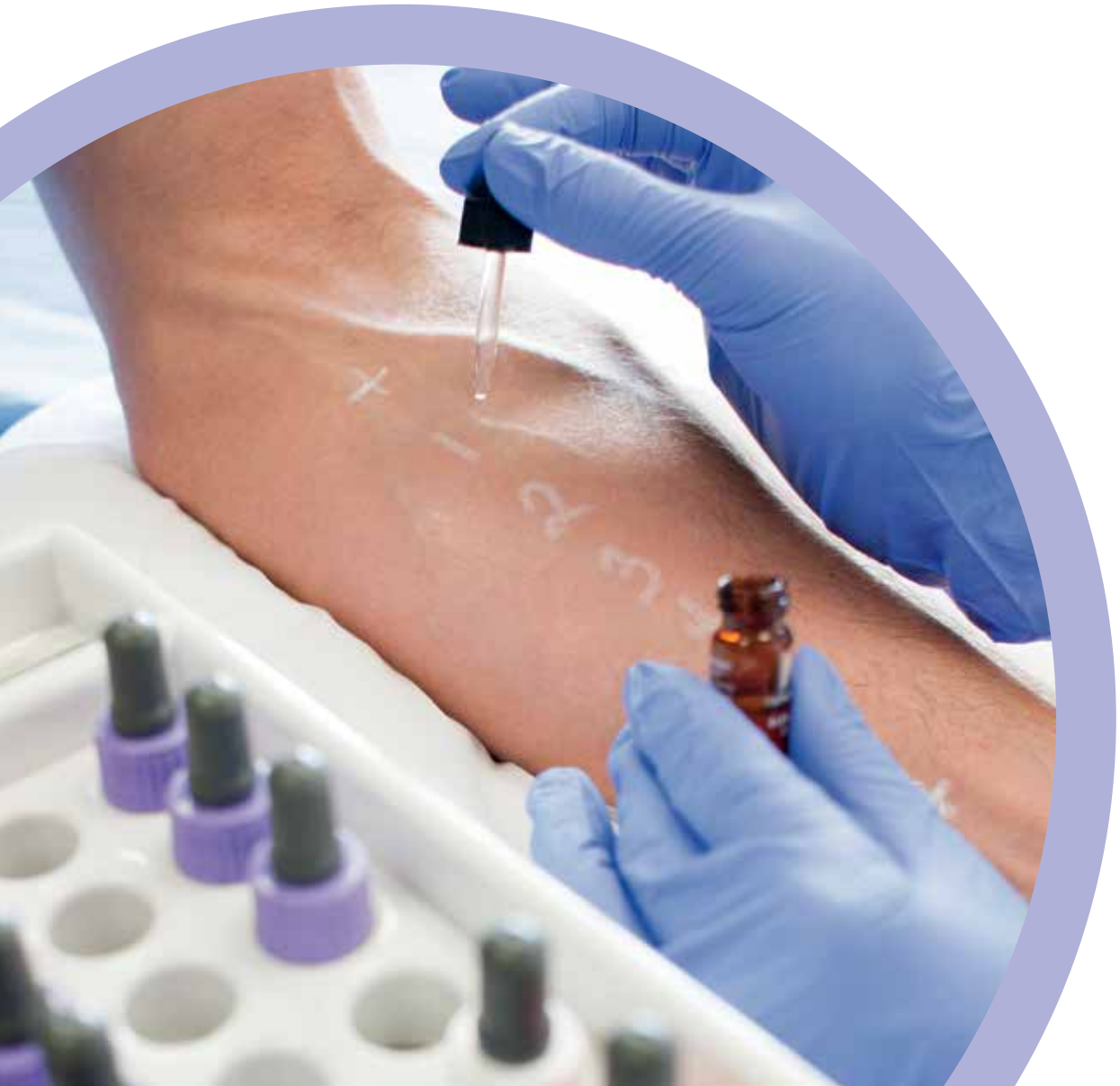
Relevant allergens for skin prick testing

The most relevant aeroallergens for Europe can be found in tab. 5. Nevertheless, routine use of a large number of skin tests without a definite clinical indication is not justified [123] especially in children because of their strongly age-dependent sensitization profiles [10]. The allergen panel to be tested should be based on patient's age and clinical history, environment and living conditions, occupation, leisure activities and varies according to regional allergen prevalence [111, 116].

Aeroallergens recommended for skin prick testing in Europe

Tab. 5: Panel of aeroallergens recommended for skin testing in European adults and adolescents (based on [116, 126, 165])

Standard prick test panel for inhalant allergens in Europe	
POLLEN	Alder *(Alnus incana* or *A. glutinosa)* Birch *(Betula verrucosa)* or mixed Betulaceae Cypress *(Cupressus sempervirens)* or other cypress pollen species Grass: one species or mixed grass pollens Hazel *(Corylus avellana)* Mugwort *(Artemisia vulgaris)* Olive *(Olea europaea)* or ash *(Fraxinus excelsior)* Pellitory *(Parietaria officinalis)* Plane *(Platanus occidentalis)* Ragweed *(Ambrosia elatior)*
MITES	*Dermatophagoides pteronyssinus* *Dermatophagoides farinae*
ANIMALS	Cat Dog
MOULDS	*Alternaria alternata* *Aspergillus fumigatus* *Cladosporium album*
INSECTS	Cockroach *(Blatella sp.)*



Implementation

Ideally, the skin prick test is performed on the volar side of the forearm. Only in exceptional cases should the skin on the back of the patient, who is lying face-down, be used for the test, e.g. if the skin on the forearm exhibits eczematous changes or in the case of small children, as the reaction on the back is more evident [166] and the sensation of pain is less pronounced in that location [88].

The intended test area should be disinfected (fig. 9A). With a pen, the test areas are marked on the skin with a distance of 3 to 4 cm in between in order to avoid cross-contamination (fig. 9B) [88, 126]. In addition, a minimal distance of 3 cm to the wrist and to the crook of the elbow should be observed.

One drop of each allergen extract should be placed beside the marked skin test area (fig. 9C). The drops should not run into each other. In order to avoid contamination, care should be taken that the drop pipette does not come into contact with the skin.

There are two possibilities with regards to further implementation

- With the simple prick test, the skin is quickly pricked vertically with the tip of a prick test lancet, through the drop (fig. 9D) [88]

OR

- With the modified prick tests, the tip of a prick test lancet is positioned, through the drop, on top of the skin at a sharp angle, then inserted flat and the lancet slightly raised so that a small quantity of the test solution can penetrate into the skin under the tip of the lancet [88]. Compared to the first option, this procedure has a higher degree of traumatization and lower reproducibility [167].

When used by experienced personnel, both tests can be regarded as of equivalent [168].

In order to avoid allergen spread, it is recommended to use a new lancet for each allergen, instead of merely wiping these off with firm pressure [169].

Excess test solution must be individually and immediately dabbed off with patients who exhibit a very strong reaction. In all other patients, this can be done after 5 to 10 minutes or shortly before the readings.

The test results should be read after 15 to 20 minutes [123]. The patient should be observed for at least 30 min after testing and be instructed to report any symptom which exceeds the test area immediately [88].

A positive test reaction manifests as a pale-yellow wheal (edema) surrounded by a red flare (erythema) (fig. 9E). The wheal should be measured (fig. 9F).
The patients are instructed to describe symptoms that manifest later at a follow-up visit [88].

If a larger number of allergens are tested than there is room for on the forearm, an additional session can take place after 2 days. If the skin test showed no reactions, the next test can take place after only 1 day [88].

Evaluation

The skin prick test is valid if

- the wheal diameter of the positive control is ≥ 3 mm
  AND
  the wheal diameter of the negative control is < 2 mm, otherwise no evaluation is possible

Then the wheal diameter of the allergen is interpreted to be

- positive if ≥ 3 mm
- negative if < 3 mm.

Pseudopodia can also occur in the event of a particularly severe reaction.

The size of the wheal does not allow for conclusions in relation to clinical relevance. [88, 116]

In the daily practice often a semiquantitative evaluation scheme (tab. 6) based on the medium wheal diameter is used [88].

If a strongly suspected specific allergy is not confirmed by the prick test, additional test methods such as the use of native materials, an intracutaneous test, determination of allergen-specific IgE or a nasal provocation test can be performed [88].

During application, the information provided by the respective manufacturer should always be given priority over the methods presented here!
The (contra-)indications specified in the section above, as well as any other parameters, are based on current German/European guidelines/position paper and are not intended to be exhaustive.

Performance of skin prick testing

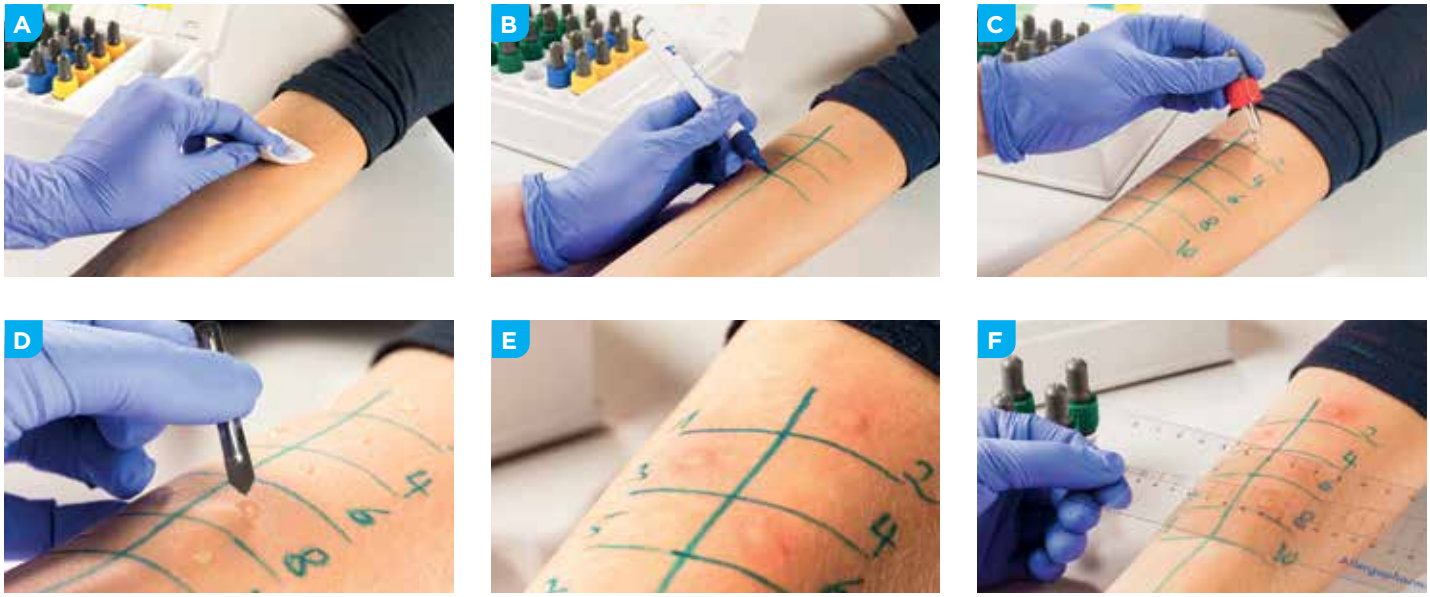


Figure 9: Performance of the skin prick test

Evaluation of skin prick testing

Tab. 6: Semiquantitative evaluation of skin prick test results based on the medium wheal diameter. This is determined by the sum of the largest wheal diameter and the respective vertical wheal diameter divided by 2 (based on [88])

Medium wheal diameter	Assessment	
no wheal (same as negative control)	Ø	negative
< 3 mm	(+)	questionable
≥ 3 mm - < 4 mm	+	single positive
≥ 4 mm - < 5 mm	++	double positive
≥ 5 mm - < 6 mm	+++	triple positive
≥ 6 mm	++++	quadruple positive

In general skin testing is easy to perform and safe. It is often performed during allergy diagnosis. But a positive skin test result alone does only indicate a sensitization against a certain allergen. Only in combination with the medical history and/or provocation testing at the nose it is possible to identify the clinically as well as therapeutically relevant allergens for the patient.

SEROLOGICAL IgE MEASUREMENT (IN VITRO DIAGNOSTICS)

In vitro diagnosis is a further diagnostic component. It is recommended when skin tests are not advisable due to contraindications [88], the skin test is positive but does not match the patient's medical history, or the skin test is negative despite suspected sensitization.

The antibodies of IgE, the molecules which play a decisive role in allergic diseases (see section Pathophysiology), primarily bind to mast cells or basophils. Therefore, the concentration of free IgE in the serum is on the nanoscale and lower than that of other immunoglobulins. Notwithstanding this, it is possible to identify and quantify the volume of free IgE [170].

Indications for determining IgE in vitro

- negative results after a skin test despite a strong suspicion of an allergic sensitization
- no extracts are available or can be manufactured for the skin test (e.g. latex, industrial chemicals)
- patients taking medication contraindicated for skin / provocation testing which cannot be discontinued (e.g. β-blocker)
- very high degree of sensitization of the patient
- increased risk of systemic reactions during skin / provocation testing
- severe dermographism, severe skin lesions
- no reaction to positive control during skin testing
- pregnancy
- infants or very old individuals
- with a strong family history of allergic reactions, umbilical cord IgE can be used as predictive of a risk factor for atopy
- quantitative results are required
- part of routine diagnosis in case of suspected bronchopulmonary aspergillosis. [170, 171]

In vitro serologic IgE measurements for allergy diagnosis include determination of

- total IgE
- allergen-specific IgE (sIgE)
  - the component-based molecular diagnosis.

Total IgE

Measurement of the total IgE level is unspecific and not appropriate per se for the specific diagnosis of allergic diseases [111], as sensitization requires evidence of specific antibodies of IgE. Total IgE, however, can potentially be used as an aid in evaluating the specific concentration of IgE: very high total IgE can cause non-specific IgE binding and hence provoke a false positive reaction to a single allergen; very low total IgE (< 20 kU/L) can result in false negative findings in the case of low-level sensitization.

Result evaluation of the total IgE measurement

- diversification of the normal values: the level is largerly age-dependent with an increase up to the age of 15 years and a decline from the 2nd through the 8th decades of life [165, 172]
- nicotine or alcohol use: influence total IgE values [173]
- elevated total IgE possible in the presence of:
  - atopic dermatitis [174]
  - immunodeficiencies [175]
  - infectious diseases such as late-stage HIV [176]
  - mycoplasma infections, pertussis and measles as well as RSV bronchiolitis [173]
  - parasitic diseases [38] or hypereosinophilic syndrome with simultaneous significantly elevated eosinophil count [173]
  - malignant diseases [173]
  - existing allergen exposure [173]

➔ high total IgE concentrations are not evidence for atopy [177]

➔ normal IgE concentrations do not exclude atopy [177].

Allergen-specific IgE

Specific IgE is the percentage of IgE antibodies in the serum which, due to its specificity, can bind to certain allergens. sIgE can be determined with in vitro tests. If the presence of a certain sIgE is verified, then the patient has a specific sensitization to the corresponding allergen. Just as in the case of the skin test, it must be determined whether the observed sensitization is clinically relevant. Only clinically relevant findings should result in clinical actions (see section Therapy) [178]. In vitro sIgE measurement is a component of allergy diagnosis and must be evaluated in conjunction with the results of the patient's medical history, also skin and provocation tests, if applicable. [173]

The quality of the allergens or extracts tested (e.g., intact conformity of the proteins, degree of purity) plays a central role in determining the sIgE [173]. In the case of standardized allergen extracts, the serum-specific IgE results correlate very closely to those of the skin test and the nasal provocations [160]. The serum IgE has a relatively short half-life in comparison with the cellular and functional active IgE antibodies in the organs, which are detected indirectly during the skin and provocation tests, and which have significantly longer half-lifes. Therefore, no complete correlation can be expected between in vitro and in vivo test results in allergy diagnosis [179]. Nevertheless, determination of sIgE in the serum and skin testing should essentially be regarded as being equivalent in allergy diagnosis [173].

Methods of IgE Determination

Nowadays, detection and quantification of total IgE and specific IgE is performed almost exclusively with so-called immunoassays which are based on the specific antigen-antibody reaction.
In traditional allergy diagnosis, the ELISA (enzyme-linked immunosorbent assay) principle is often used. This involves the antigens or allergens binding to a solid phase. Subsequently, the patient's serum with its diverse IgE antibodies is added. During the incubation period of 30–60 minutes, the sIgE have the opportunity to bind to their matching allergens. In subsequent washing steps, unbound or only loosely bound IgE molecules are removed. During the next step, enzyme-linked secondary antibodies (detection antibodies) to IgE are added. They bind to the Fc end of the bound IgE molecules. After another incubation period, unbound enzyme-marked anti-IgE is washed off. The bound enzyme can be measured by means of a color or fluorescence reaction. The more sIgE was contained in the serum, the more was bound, and the more intense is the color or fluorescence reaction. [5, 38, 111, 123, 170, 180]

The popular ImmunoCAP procedure is also based on this principle. Microarray technology or multiplex-based in vitro procedures are used increasingly often [5].

Component-based diagnosis

These molecular methods identify IgE antibodies which bind to certain allergen components. The first allergen component discovered was the major birch pollen allergen Bet v 1. The determination of the individual molecular sensitization pattern is helpful with differentiating between real double sensitizations and cross-reactivities especially in the case of hymenoptera venom or food allergies. Moreover, it is possible to formulate a risk profile for the occurrence of anaphylactic reactions in food allergies. Component-based diagnosis is cost-intensive and not suitable for all allergy patients. Hundreds of allergen components have been identified, however their clinical relevance is often unknown. The resulting complexity of the data can be a challenge. Meanwhile, the EAACI published a Molecular Allergology User`s Guide, which can help to integrate the component resolved diagnosis into the clinical practice. [181–183]

The determination of sIgE plays a role when in vivo diagnosis at the skin or the nose is impossible (e.g. respective allergen extracts are not available or when patients show contraindications for performing in vivo diagnosis). The component-based diagnosis allows to identify sensitizations to specific marker- or cross-reactive allergens. In food-allergic patients it may help to evaluate the risk for severe systemic reactions.

PROVOCATION TEST (IN VIVO DIAGNOSTICS)

Through a provocation test, allergic symptoms can be triggered on the membranes of the nose, eyes and bronchi. Provocation tests are indicated if the results of previous tests (usually skin prick test, in vitro tests) do not coincide with the patient's medical history, the clinical relevance has not been clarified, or additional significant results are required to determine therapy. Therefore, potential outcomes should be derived from the result. For the provocation test, the symptoms are artificially reproduced on the organ where they are manifesting. [123, 184]

BRONCHIAL PROVOCATION TEST (BPT)

The triggering of a bronchial obstruction through the application of an allergen serves to substantiate the diagnosis of allergic asthma. Due to the potential risks, the indication must be strictly confirmed and the test, if applicable, be performed under inpatient conditions. BPT is routinely performed in the investigation of suspected occupational sensitizations or as a research tool [185]. It is recommended only to perform it in specialized centers with demonstrable expertise and experience in a clinical setting [185, 186].

CONJUNCTIVAL PROVOCATION TEST (CPT)

The CPT with allergens is performed by instilling an allergen solution on the ocular conjunctiva to elicit an IgE-mediated allergic reaction of the ocular surface mucosa. CPT is usually conducted for suspected localized eye allergy but is sometimes also helpful to confirm nasal allergy. It can be used instead of nasal provocation testing even if the patients do not report ocular allergic symptoms. CPT is evaluated by symptoms of itching, tearing redness and conjunctival edema [186]. It must be performed by well-trained and experienced staff, to avoid complications [187]. Patients should be fully asymptomatic and contact lenses have to be removed 72 hours before [187].

In the last decades the authorization requirements in Europe rose also for allergens for diagnostic tests. Therefore, offering a comprehensive panel of allergens for in vivo diagnosis was no longer cost-effective for manufacturers because expenses only for authorization maintenance far exceed their related revenues. Consequently, the manufacturers in Europe significantly limited their allergen portfolio, [188] especially for authorizations of test solutions for CPT.

NASAL PROVOCATION TEST (NPT)

The NPT constitutes an important test method in allergological-rhinological diagnosis. It is considered as a procedure with a high level of specificity and sensitivity in testing for allergic diseases and can be performed on an outpatient basis.

The NPT focuses on the evaluation of subjective symptoms and the objective measurement of airway resistance (rhinomanometry), the number of sneezing attacks and the volume of nasal secretion. However, extranasal symptoms such as in the eyes, palate or lungs are also included in the assessment [189]. Additionally, an analysis of the inflammatory mediators contained in the nasal secretion can be performed. [123]

Knowledge of the nasal cycle is indispensable for the application and evaluation of nasal provocation testing [115].

A previous exposure to allergens may influence the results in NPT. Therefore, NPT using seasonal allergens should be performed not earlier than 4 weeks after the respective pollen season. When NPT with perennial allergens is planned (e.g. house dust mites, molds, animal allergens) the patient should have only mild symptoms which do not interfere with the results. (190)

Indications

- diagnosis of suspected persistent or intermittent allergic rhinitis, local allergic rhinitis or occupational rhinitis (94, 190)
- confirmation of allergic rhinitis, especially to identify the clinically relevant allergens in polysensitized patients (189, 191)
- inconsistent or ambiguous results of previous allergy diagnosis (e.g. medical history, skin test, sIgE) (64, 191)
- suspected occupational allergic rhinitis with the use of workplace-specific dusts (189, 192)
- confirmation of allergic asthma if the bronchial provocation test is too risky or when the corresponding BPT is negative (189, 193)
- monitoring clinical efficacy during AIT (190).

Contraindications

Absolute contraindications

- acute inflammation of the nose and paranasal sinuses (190)
- pregnancy (189, 190)
- severe general diseases, e.g. patients with cardiopulmonary diseases, reduced lung capacity, malignant diseases, autoimmune diseases (189–191)
- prior severe anaphylaxis (190)
- extremely high grade of sensitization (190)
- severe or uncontrolled asthma; severe chronic obstructive pulmonary disease (COPD) (190, 191, 193)
- anatomical nasal pathologies, such as advanced polyposis nasi, perforated septum, etc. (5, 194)
- systemic immunotherapy (190).

Relative contraindication

- small children ≤ 5 years (190, 195, 196)
- unstandardized allergen extracts (190).

Contraindication which may cause a delay

- nasal surgery less than 6 to 8 weeks prior (5, 189, 190, 193)
- vaccination within the past 7 days (94, 190)
- consumption of alcohol or cigarettes 24–48 hours prior (190, 191, 197)
- any viral or bacterial infection in the last 4 weeks (94, 190)
- acute allergic period or exacerbation at any organ (190, 193).

Materials

- **Allergens:** available as ready-to-use solutions or as freeze-dried lyophilizate which should be used following the manufacturers' information (190)
- **Negative control:** allergen-free solvent; in order to detect an unspecific reaction, the negative sample is applied to the nasal membrane before allergen testing can begin (190, 193)
- **Rhinomanometer:** if available; use a new nasal adapter for each patient and each allergen (190).

Commercially available allergen extracts for skin prick testing should not be used for NPT since most contain glycerol which can cause unspecific reactions in the nose (191, 198).

Methods for evaluation

Evaluation of NPT is performed using objective measurements of the nasal breathing resistance via rhinomanometer and/or subjectively semi-quantitative by means of symptoms which are documented by the patient and/or the investigator (190).

The following are some of the objective evaluation resources for assessing the nasal symptoms (190)

- active anterior rhinomanometry (AAR) - which is recommended by the committee on standardization of rhinomanometry (191, 199)
- peak nasal inspiratory flow (PNIF), in other words, the measurement of the inspiratory air flow of the nose
- acoustic rhinomanometry (AcRh)
- 4-phase rhinomanometry (4PR).

There are different semiquantitative, subjective symptom scoring systems for NPT, for example

- scoring system evaluating nasal and distant symptoms at the eyes, palate, ears, lower airways and skin proposed by the ENT section of the German Society for Allergology and Clinical Immunology (DGAKI). A maximum of 6 points can be achieved (tab. 7) [189, 200]
- Likert scale: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms [201]
- visual analog scale (VAS): the severity of the symptoms is indicated on a horizontal axis from 0–100 mm; 0–30 mm = mild, 31–70 mm = moderate, 71–100 mm = severe [202, 203]
- total nasal symptom score (TNSS): a scale on which, similar to the Likert scale, points are assigned for the severity of the symptoms with regard to: rhinorrhea, nasal obstruction, sneezing, itchy nose. Maximum 12 points [190]
- Lebel symptom score scale [191, 204]
- Linder symptom score scale [191, 205].

In 2016 the EAACI originated a task force to develop a position paper on the standardization of nasal allergen challenges which was published in 2018. This task force recommends to use the visual analog scale (VAS) for symptom scoring (see above). [190]

According to this the positivity criteria for NPT results are

a) subjective measures are clearly positive, i.e. the VAS symptoms are ≥55 mm; Lebel score, Linder score or TNSS increased for at least 5 points
b) objective measures are clearly positive, meaning a flow decrease of ≥40 % in PNIF, nasal cross-sectional area 2 (CSA-2) decrease of ≥40 % in AcRh, flow decrease of ≥40 % at 150 Pascal in AAR, or a ≥40 % increase in logarithmic effective resistance in 4PR
c) two criteria, i.e. one objective AND one subjective measurement, are moderately positive (for subjective measures: VAS symptoms ≥23 mm, Lebel score, Linder score or TNSS increased for at least 3 points; for objective measures: flow decrease of ≥20 % in PNIF, decrease in sum of 2-6 cm^3 ≥27 % bilaterally in AcRh, flow decrease of ≥20 % at 150 Pascal in AAR, or ≥20 % increase in logarithmic effective resistance in 4PR. [190]

Symptom scoring for NPT

Tab. 7: Scoring system for evaluation of clinical symptoms after nasal provocation (based on [189, 206])

Symptom	Severity	Score (Points)
SECRETION	No secretion	0
	Little secretion	1
	Heavy secretion	2
IRRITATION	0-2 sneezes	0
	3-5 sneezes	1
	> 5 sneezes	2
EXTRANASAL SYMPTOMS	None	0
	Lacrimation and/or itchy palate and/or itchy ears	1
	Conjunctivitis and/or chemosis and/or urticaria and/or coughing and/or dyspnea	2

Procedure

When making an appointment for NPT the patient should be informed that some medications may influence the results in NPT and which washout periods are valid (tab. 8). NPT should preferably be performed in the morning. [190]

The washout periods listed in tab. 8 are often related to studies where medications are administered for short term. It is possible, if a patient is taking multiple drugs, that alone have a minor effect, the combination of these drugs could suppress the nasal response. There are no data available for combination preparations containing at least one of the active substances mentioned above.

Washout periods before NPT

Tab. 8: Medications which interfere with the nasal reactivity and have to be discontinued with a respective time interval (washout period), since they cause a false-negative NPT result

Some medications listed above should not be discontinued without assistance from the prescribing provider (e.g. antidepressants, corticosteroids).
Ideally, the allergist should discontinue medications for the minimal time necessary to produce accurate nasal provocation test results and avoid cessation of drugs that do not affect the testing [129].
This table makes no claim to completeness.

Medication	Recommended washout period before NPT
α-sympathomimetics – nasal	
Oxymetazoline, Xylometazoline	1 day [206]
Antihistamines – nasal	
Azelastine	24 hours [130]
Levocabastine	3 days [130]
Antihistamines – oral	
Azelastine, Dimetindene	7 days [130]
Cetirizine, Clemastine	3 days [130]
Fexofenadine	2 days [130]
Loratadine/Desloratadine	2-3 days [130]
β_2-agonists - inhaled	
Fenoterol	8 hours [130]
Salbutamol	6-8 hours [130]
Terbutaline	None [130]
β_2-agonists - oral	
Fenoterol, Salbutamol	2 days [130]
Terbutaline	None [130]
β_2-agonists - injective	
Reproterol, Salbutamol	None [130]
Theophylline (short to medium long acting)	12–24 hours [130]
Theophylline (retard preparations)	2 days [130]
Corticosteroids – nasal	
Beclomethasone, Flunisolide, Fluticason-propionate, Triamcinolone	14 days [130]
Mometasonfuroate	7 days [130]
Corticosteroids – inhaled	
Flunisolide	14 days [130]
Corticosteroids – systemic	
> 10 mg/d prednisolone equivalent	7 days [206]
Mast cell stabilizers	
Sodium cromoglycate	3 days [200]
Ketotifen	3 days [130]
Tricyclic antidepressants	2-3 weeks [191]

Preparation

- Room without contamination of any substances (e.g. methacholine, allergens). Recommended room temperature of 20 ± 1.5°C, humidity of 40-60 %
- patient acclimatization for at least 15 minutes
- examination of nasal anatomy and nasal air passage. (190)

Baseline measurement

➔ Relevant to assess the nasal ventilation before control and allergen solutions, i.e. comparing the initial value with the results with control and allergen.

- Determine baseline value objectively and subjectively. (190)

Control provocation

➔ Relevant because some allergen solutions contain preservatives which may irritate the nasal mucosa.

- Patient clears nose by sniffing, inhales and holds breath
- apply negative control provocation (NaCl 0.9 % + preservative (phenol)) into the nose
- patient exhales through the nose to avoid inhalation of the negative control
- 10 minutes waiting period
- determination of the blank value on both sides by rhinomanometry and/or documentation of symptoms. Provocation only possible if both sides of the nose are clear, i.e. the control solution causes <50 % of the positivity criteria (see page 39/40, "methods for evaluation"). If the reaction is ≥50 % of the positivity criteria the test must be postponed (190).

Allergen provocation

- Patient clears nose by sniffing, inhales and holds breath
- apply test solution giving 2 puffs in both nostrils: one in the inferior meatus and one on the direction of the middle turbinate
- patient exhales through the nose to avoid inhalation of the allergen
- 10 minutes waiting period
- measuring with rhinomanometry and/or documentation of symptoms. Symptoms should be documented once, rhinomanometry should be performed three times in a row to eliminate technical problems. In case of positive results stop testing
- in case of unclear result repeat rhinomanometry and/or documentation of symptoms after 10 minutes. (190)

Follow-up

- Patient has to be observed for at least 30 minutes until reaction ceased
- patients should be advised that late phase reactions may occur and receive rescue medication. (190)

If the allergen tested was negative, then a second one at most can be tested on the same day (123, 190, 193, 207–209).

When rhinomanometry is used, a "correct positive" reaction is expected in approximately 80 % of cases. If there are doubts as to the normal reactivity of the nasal membrane in a patient with a negative reaction, unspecific provocation can be performed with a histamine solution. (189)

Possible reasons for false-positive results

- High allergen concentration
- infectious or allergic process in the previous 2 – 4 weeks
- lack of control of irritant reactions due to impurities or preservatives of allergen, e.g. phenol, glycerol or benzalkonium chloride
- drugs interfering with the test results
- recent allergen exposure, contamination of the examination room or allergen
- irritating pH (<5 or >8) or hypo-/hyperosmolality in extracts which were individually prepared
- lack of adaption to room climate. (190, 191)

Possible reasons for false-negative results

- Concomitant medication that interferes with the test result which was not discontinued during the suggested washout period (tab. 8)
- nasal surgery in the previous 8 weeks
- test solution with too low concentration or expired shelf-life
- lack of adaption to room climate
- nasal polyposis. (190, 191)

Fig. 10 shows the schematic procedure of nasal provocation testing based on the recommendation made in the EAACI position paper (190) which is described before.

During application, the information provided by the respective manufacturer should always be given priority over the methods presented here!
The (contra-)indications specified in the section below, as well as any other parameters, are based on the German and European guidelines and/or position papers and are not intended to be exhaustive.

Procedure of nasal provocation testing

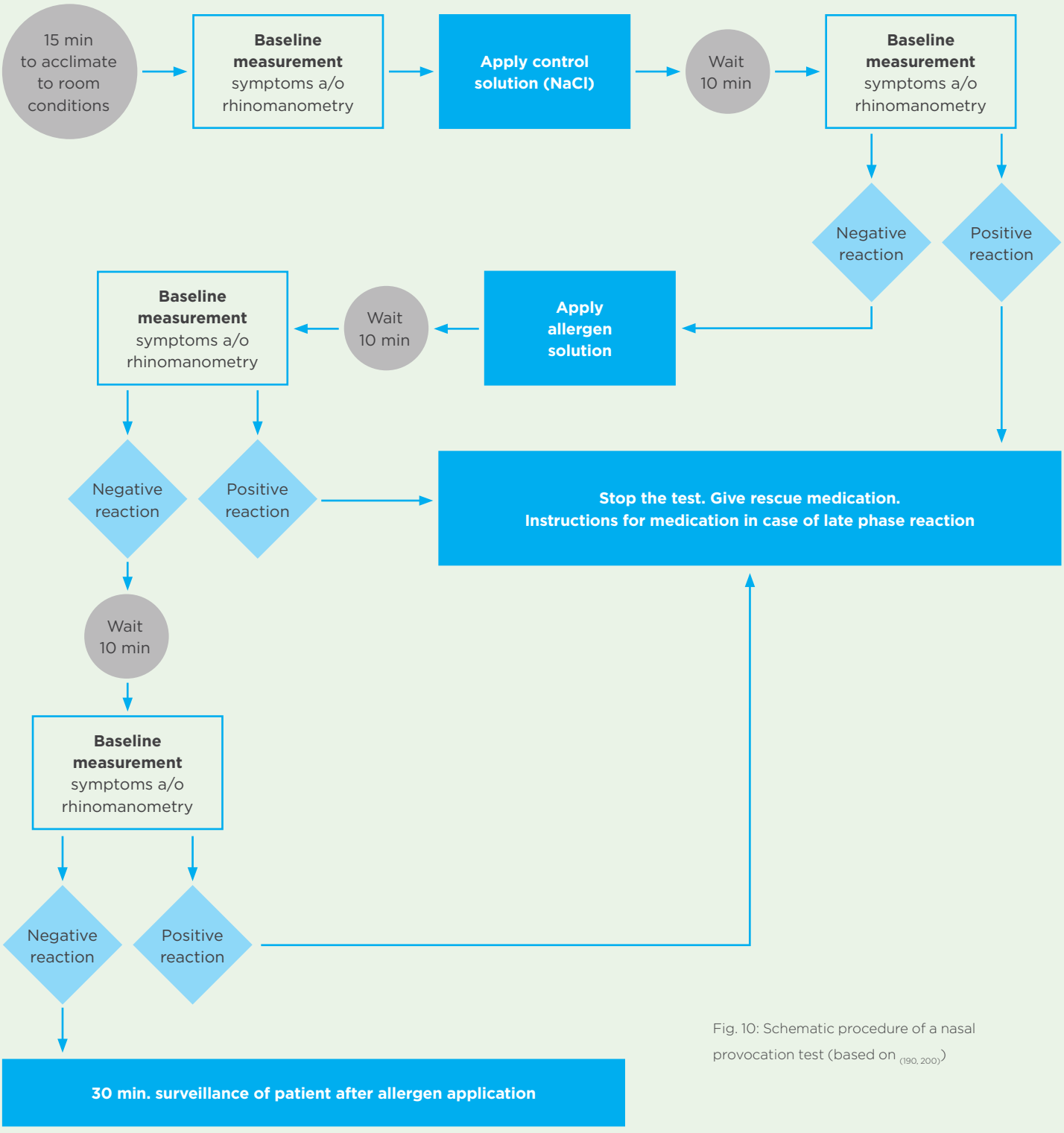
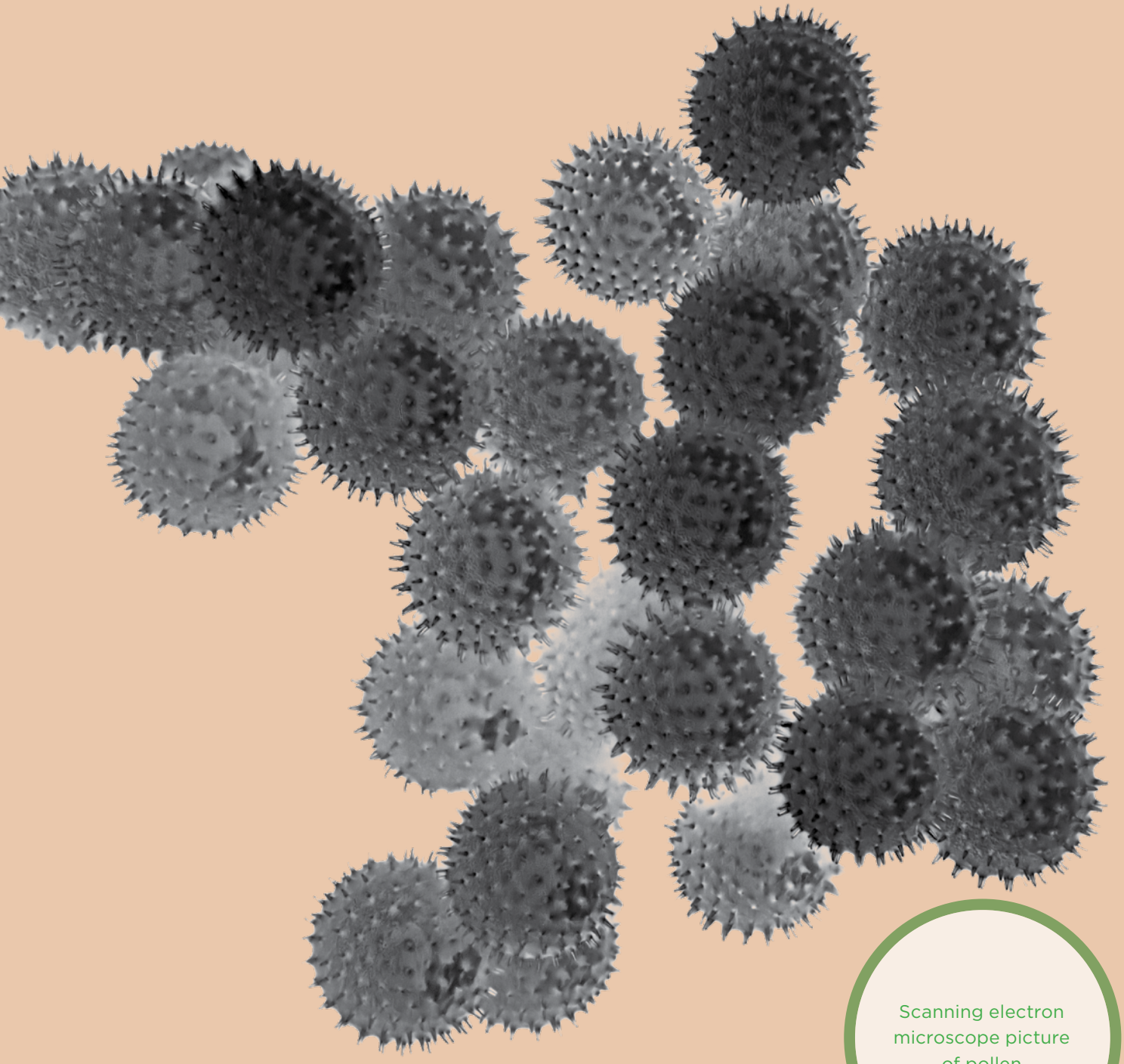


Fig. 10: Schematic procedure of a nasal provocation test (based on [190, 200])

Provocation testing is indicated when preceding skin testing or in vitro diagnosis do not correlate with patient's medical history or the clinical relevance of the allergens must be confirmed for therapeutic decisions. NPT is often used for confirmation of perennial allergic rhinitis. BPT should be performed in specialized centers.

THERAPY



Scanning electron microscope picture of pollen

There are several options to manage allergic diseases: allergen avoidance, symptomatic treatment and allergen immunotherapy (AIT) [23].

Allergen avoidance means to reduce the allergen load of the environment. For symptomatic treatment e.g. antihistamines, corticosteroids, leukotriene-receptor antagonists or mast cell stabilizers are used. AIT is the only causal treatment option for allergic diseases [210, 211] and therefore has effects beyond cessation of therapy [40, 212].

The different treatment options are prescribed in the following chapters.

ALLERGEN AVOIDANCE

An essential element in the management of allergic conditions is allergen avoidance where possible. This requires the knowledge of the patient's specific spectrum of clinically relevant allergens. Measures for environmental control should be comprehensive, consequent and long-term, to reduce the pollution sustainable. Allergy sufferers often have to decide whether to part with habits they hold dear or maintain and/or restore their health. (200)

For pollen-allergic patients it is generally nearly impossible to completely avoid the allergens because of their ubiquitous occurrence but the contact should be at least reduced. Patients should be advised to remove their clothes and shower immediately when returning home. Pollen may be sticking to the clothing, skin and hair. The bedroom is advised to be a room with low level of allergens. Therefore, windows should be closed during the pollen flight and before the patients go to bed. Basic air-conditioning filters are able to filter out large pollen particles. If possible, patients should shift outdoor activities from the morning to the evening when the pollen count generally is lowest. (213)

House dust mites are the second leading source of allergens after pollen, and they trigger symptoms throughout the year. House dust mites are commonly present in human dwellings and are especially abundant in mattresses, sofas, carpets, and blankets. Bedding, pillows, and stuffed animals may also carry relevant amounts of allergen. (38, 94) Reducing allergens in these items should therefore be part of the overall bedroom allergen load reduction effort. In fact, optimum reduction of house dust mite allergen exposure in the bed(room) can only be achieved through simultaneous mattress, pillow, and bedding allergen minimization. Good compliance depends on the use of encasings that minimize impairment of sleep quality. This is achieved through the use of breathable encasings that are permeable to water vapor. (214–217)

Pets are a case in point. They are a reservoir of a multitude of allergens. The most effective intervention is to remove the animal from the allergic patient's home. If this is not an option without causing substantial psychological/mental problems, direct contact should be avoided, and the animal should at least be banned from beds and bedrooms. Patients should also be aware of possible exposure in public transportation, schools, and public places. (38, 213)

Mold spores may also be relevant allergens (201), and their detection in rooms should result in appropriate action. The most important measure is to let in enough fresh air and reduce humidity levels. Potting soil also contains molds, so potted plants may need to be removed from bedrooms or the entire home. Mold-contaminated foods should be removed immediately and containers cleaned. What may need to be done about mold-infested construction materials should be decided by specialists on site. (201–203)

Occupational allergies are a particular challenge. Examples include latex allergies among healthcare professionals, animal allergens in laboratories or veterinarian offices, and food or fungal allergens in the food-processing industry. Suitable protection may allow affected patients to stay in their occupation. Since the reduction in allergens may not be sufficient, strict avoidance sometimes requires a change of occupation. (23)

Allergen avoidance by the control of the environment is generally the first treatment of choice to reduce allergic symptoms. But often the methods are not sufficient or only difficult to implement that it is necessary to start symptomatic treatment or AIT.

SYMPTOMATIC TREATMENT

A symptomatic treatment is often used primarily to control the patients' allergic symptoms [108]. The effect of those medications is not long-lasting und they must be used repeatedly, since they do not affect the underlying mechanism [38]. Especially, symptomatic treatment does not have effects that persist over the treatment duration [219, 220]. Moreover, surveys in the USA and Great Britain showed, that up to 22 % of children and 62 % of adults with an allergic rhinitis reported only partial or bad improvement when treated with symptomatic medication only [221, 222].

ALLERGIC RHINITIS

Allergic rhinitis is primarily treated with symptomatic medication like antihistamines, topical corticosteroids, mast cell stabilizers or leukotriene-receptor antagonists.

H1-antihistamines block H1-receptors to prevent histamine binding to the effector cells thereby inhibiting the proinflammatory effects of histamine. This in turn prevents the development of allergic symptoms. Antihistamines are often used orally, but they are also available for topical use on nose and eyes. The first-generation oral antihistamines were able to cross the blood-brain barrier and caused unwanted sedative side-effects. Therefore, they are no longer recommended for the treatment of allergic rhinitis. Meanwhile, newer generations are available without sedative effects. Intranasal antihistamine sprays may be used as the first or second treatment option in allergic rhinitis. They may be effective within 20 minutes, require twice a day dosing and reduce all allergic symptoms at the nose but have a reduced effect on nasal obstruction compared to nasal corticosteroids. Also oral antihistamines are less effective in reducing nasal obstruction than nasal corticosteroids. [38, 94, 108, 218, 223].

Corticosteroids have a very broad spectrum of activities. A key activity is inhibition of the synthesis of inflammatory mediators. Intranasal corticosteroids are currently the most effective class of symptomatic medication available for the treatment of allergic rhinitis, especially because they are effective at improving all symptoms at eyes and nose. They are particularly indicated for nasal congestion or frequent symptoms. Oral corticosteroids are not recommended for the routine treatment of allergic rhinitis. They may be used for a few days (3 to 5 days) to control severe allergy symptoms, or to gain control of symptoms during acute exacerbation, but they are associated with substantial long-term side effects. Injectable corticosteroids are not recommended because of the possibly systemic side-effect. [38, 218, 224]

Mast cell stabilizers such as sodium cromoglycate, nedocromil, and ketotifen reduce calcium influx, thereby decreasing the degranulation of histamine from mast cells and hence the development of allergic symptoms. However, if the degranulation has already occurred, mast cell stabilizers are theoretically not useful. So, they are best used prophylactically before allergen exposition starts to prevent onset of symptoms. Mast cell stabilizers have a fast onset of action, but the effect is smaller than with other medications used for the treatment of allergic rhinitis. They are only recommended for short-term use. [38, 224, 225]

Leukotriene-receptor antagonists bind with high affinity and selectivity to cysteinyl-LT1-receptor, a leukotriene-receptor subtype to block the potent proinflammatory leukotriene D4. Leukotriene-receptor antagonists are as effective as oral antihistamines but inferior to intranasal corticosteroids in treating seasonal allergic rhinitis. [38, 53, 226, 227]

Intransal α-sympathomimetics (decongestants) are primarily used for the acute treatment of allergic rhinitis. They act on α-adrenergic receptors and lead to vasoconstriction of the nasal mucosa, which can relieve nasal congestion. Because of the side-effect profile, especially when used for longer periods, they are generally taken for short-term only. [108, 218]

Approximately 40 % of patients with allergic rhinitis use two or more medications although the additional effect of a second preparation could not be confirmed in many clinical trials [228, 229]. However, a nasal spray containing a combination of an antihistamine and a corticosteroid shows a rapid onset of efficacy and is more effective than the single substances alone [108, 230].

ALLERGIC CONJUNCTIVITIS

Artificial tears or saline solutions may be used for slight symptoms. They improve the barrier function of the conjunctiva and wash out the allergens [231, 232]. Antiallergic eye drops are the basic treatment for allergic conjunctivitis. Topical antihistamines are especially effective in rapidly reducing the symptoms in the acute phase of conjunctivitis, but duration of effect is limited [232]. In contrast, topical mast-cell stabilizers are mostly not effective before 10 to 14 days so that treatment has to be started early before the expected allergen exposition [43, 232]. Topical α-sympathomimetics reduce conjunctival hyperemia, chemosis and redness but should be prevented because of the expected rebound hyperemia [231, 232]. Topical nonsteroidal antiphlogistics reduce itching and conjunctival hyperemia [232]. Corticosteroid eye drops may be used in more severe symptoms. They have a rapid onset of action, since they suppress the acute phase of the inflammation but also influences the chronic persistent inflammation processes. Because of the side effect profile corticosteroid eye drops should be used only for short-term [231, 232]. When intranasal corticosteroids are used for the treatment of nasal symptoms in seasonal allergic rhinitis often symptoms at the eyes are also improved [41, 233]. Systemic antihistamines have a lower effect on the symptoms at the eyes than at the nose [231]. Often several medications are combined to reduce the symptoms effectively, some are available as combination preparations [232].

ALLERGIC ASTHMA

The long-term goals of asthma management are to achieve good symptom control in order to prevent exacerbations. In control-based asthma management, treatment is adjusted in a continuous cycle taking into account symptoms, lung-function, exacerbations, side-effects and patient satisfaction. Asthma can be well controlled, not well controlled or very poorly controlled. A stepwise approach was developed for different age groups that recommend medications depending on the level of asthma control. Asthma control should be retained with the smallest number of anti-asthmatic medications in the lowest dose possible. There are three categories of pharmacological options for long-term treatment of asthma: controller medication for regular maintenance treatment, reliever medications for short-term prevention of exercise-induced bronchoconstriction and add-on therapy for patients with severe asthma. Most anti-asthmatics are available for inhalation. Inhaled corticosteroids are the main controller medications because they affect the underlying inflammation. Short-acting $ß_2$-agonists (SABA) may be used as reliever. They are highly effective for the quick improvement of asthma symptoms, but they should be reserved for patients with occasional daytime symptoms of short duration. Leukotriene-receptor agonists may be appropriate for initial controlled treatment for patients who experienced intolerable side-effects from inhaled corticosteroids. Long-acting $ß_2$-agonists (LABA) should not be used without inhaled corticosteroids because of the risk of exacerbations. [234, 235]

For several years, biologicals are available for patients suffering from severe asthma. Anti-IgE is a recombinant, humanized monoclonal antibody that forms complexes with free IgE, blocking its interaction with mast cells and basophils resulting in a lowering free IgE levels in the circulation. Anti-IgE (omalizumab) can be prescribed as supplementary treatment for patients with severe persistent IgE-mediated allergic asthma to perennial aeroallergens to achieve better asthma control, when the patients had severe asthma exacerbations despite daily treatment with high-dose inhaled corticosteroids and inhaled LABA. [5, 38, 236] The clinical data so far available confirm that omalizumab may be a valuable option as add-on to allergen immunotherapy especially in the dose-escalation phase, in which adverse events are more commonly expected [237].

Symptomatic anti-allergic drugs for the treatment of allergic rhinitis and conjunctivitis have different mechanisms of action which typically result in blockade of allergic/inflammatory mediator cascades. Generally, they are the first treatment option in allergic patients. The main objective of treating patients with allergic asthma is reaching asthma control. Therefore, primarily inhaled anti-asthmatic medications are available with inhaled corticosteroids generally being the basis of long-term treatment.

ALLERGEN IMMUNOTHERAPY (AIT)

AIT is a well-documented treatment in IgE-mediated allergic diseases. As a therapy with disease-modifying effects it is tolerable and effective in the treatment of allergic rhinitis, asthma and hymenoptera venom allergy [212]. The mechanisms are multiple and complex, by administration of increasing doses of the allergen extract the immune response to the allergen will be modified. Specific blocking antibodies, tolerance-inducing cells and mediators are built to prevent further exacerbations of the specific immune response, to block it and to reduce the inflammatory response in the tissue [238]. Because AIT modifies the immune-system it has preventive effects which are important rationales for initiating AIT early in childhood and adolescents [212].

The first paper on AIT was published by Noon and Freeman in 1911. These authors used pollen extracts for subcutaneous administration [239]. This treatment modality has since been continuously refined. Today AIT is primarily used subcutaneously (SCIT) and sublingually (SLIT) for the treatment of IgE-mediated allergic diseases caused by aeroallergens.

Interesting!
An investigation based on meta-analyses "provided indirect bus consistent evidence that SCIT is at least as potent as symptomatic treatment in controlling the symptoms of seasonal allergic rhinitis as early as the first season of treatment" [240]. The meta-analyses had to include 5 or more randomized, double-blind, placebo-controlled trials of SCIT, the nasal corticosteroid mometasone furoate, the leukotriene-receptor antagonist montelukast or the antihistamine desloratadine in patients with seasonal allergic rhinitis (Fig. 11).

Effect of SCIT versus symptomatic treatment in seasonal allergic rhinitis in the first treatment year

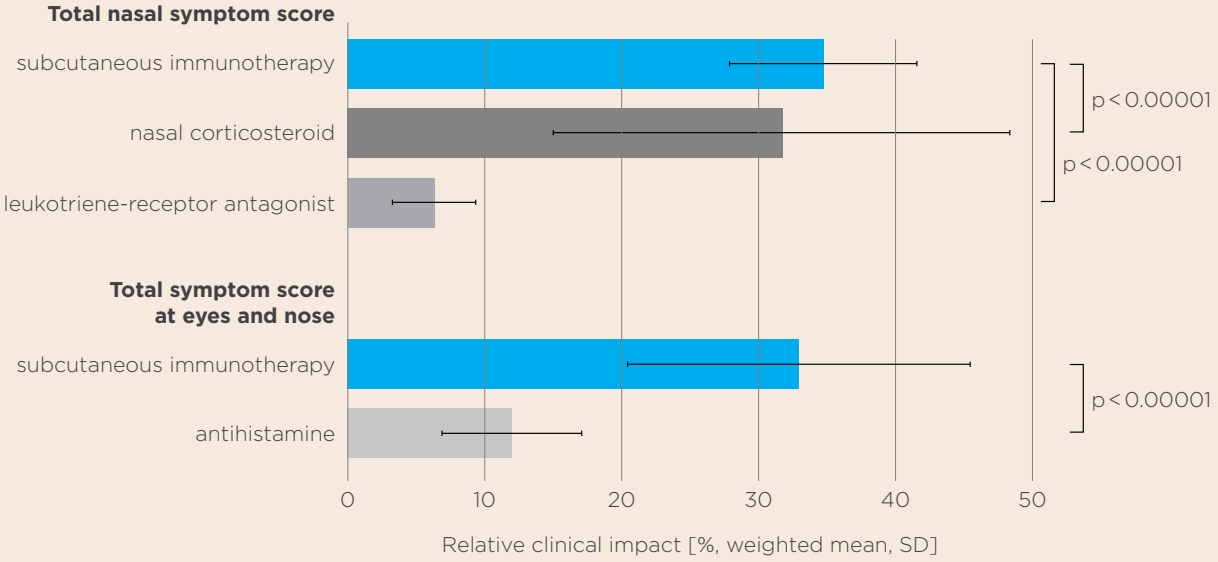


Fig. 11: Relative clinical impact (RCI) calculated as the percentage reduction in total nasal symptom score and total symptom score at eyes and nose obtained with active treatment compared with placebo for subcutaneous immunotherapy, the nasal corticosteroid mometasone, the leukotriene-receptor antagonist montelukast and the antihistamine desloratadine in the first treatment year. Shown for weighted mean RCI with standard deviation (SD) (based on [240])

MECHANISM OF ACTION

The mechanisms during AIT are complex and AIT works through several immunological pathways. However, the detailed mechanism is not yet fully understood [241]. The mechanisms of SLIT and SCIT have been shown to be similar [242]. Fig. 12 shows the immunological mechanisms of AIT on cellular level.

After AIT administration, the immune system reacts similar like after contact with the native aeroallergens. The allergens diffuse into local tissue where they are taken up by regional dendritic cells, which thereafter migrate into the local lymph nodes [212, 243]. The dendritic cells process the allergen to fragments (peptides) which form a complex with molecules of the MHC class II.

Mechanism of action of AIT

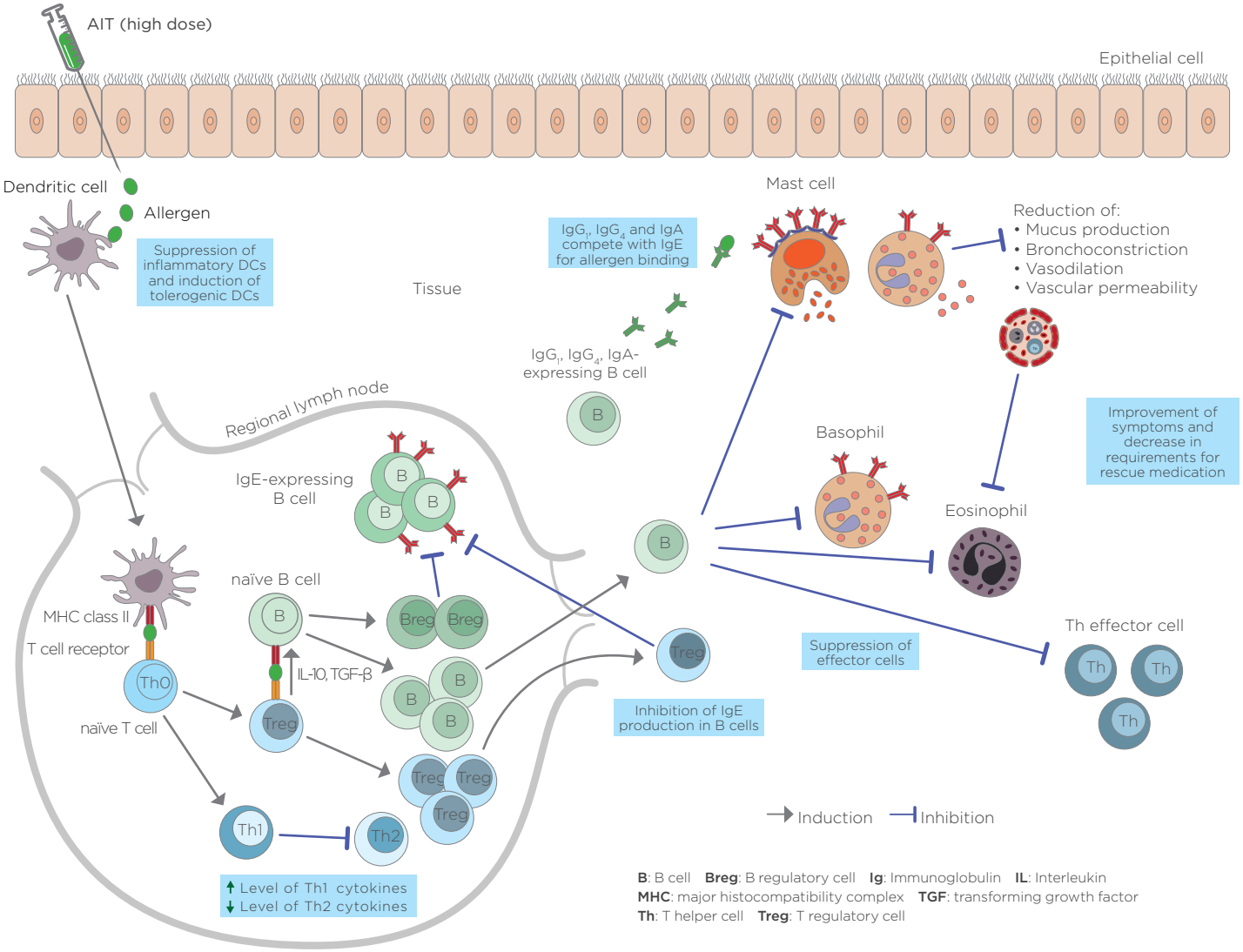


Fig. 12: Mechanism of action of AIT on cellular level (based on [19, 20, 243, 245])

This complex is presented on the surface of the dendritic cells and is recognized by naïve T cells via their T cell receptor. In contrast to the natural allergen which induces differentiation of T cells into Th2 cells in the allergic prone subject (fig. 2 and 3) the high allergen doses administered by AIT adjust the function of the dendritic cells in favor to promote immune deviation from the Th2 immune response towards a more balanced or Th1 response resulting in a decrease of Th2 cytokines like IL-4, IL-5, IL-9 and IL-13 [20]. Another important step during AIT is the generation of allergen-specific T regulatory (Treg) cells that are able to produce anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) as well as B regulatory (Breg) cells [243, 244]. Treg cells inhibit the allergen-specific IgE production and induce IgG_4 production in B cells [19]. B cells additionally promote the production of IgG_1, IgG_4 and IgA [20]. The allergen-specific IgG, especially IgG_4 competes with IgE for allergen binding since they might be directed against the same epitopes [20, 245]. This prevents cross-linking of high-affinity IgE receptors on basophils and mast cells thereby inhibiting histamine release and degranulation [20]. This in turn is followed by a reduction in mucus production, bronchoconstriction and vascular permeability, thereby reducing allergic symptoms [228]. Inhibition of vascular permeability again results in a decreased recruitment of effector cells into the tissue of the allergic reaction leading to a reduction of tissue inflammation [20]. Moreover, Treg cells suppress allergic responses by suppression of mast cells, basophils and eosinophils as well as effector T cells [243]. Treg cells may also interact with resident tissue cells and contribute to tissue remodeling [19].

A chronology of immunological changes during AIT was observed. Although there is significant variation between subjects and protocols, right after the first administration of allergens with native-like structures, an early decrease in mast cell and basophil degranulation and a decreased tendency for systemic anaphylaxis are observed. This is followed by generation of allergen-specific Treg cells and suppression of both allergen-specific Th1 and Th2 cells, and maybe of other effector cells. An early increase and a very late decrease in specific IgE levels are observed. In particular, the IgG_4 level shows a relatively early increase that is dose dependent. In some studies allergen-specific IgG_1 and IgA levels also increase. A significant decrease in the allergen-specific IgE/IgG_4 ratio occurs after several months. A significant decrease in type I skin test reactivity is also observed relatively late in the course of SCIT. A decrease in tissue mast cell and eosinophil numbers and a release of their mediators and decrease in the late-phase response is observed after a few months. [326, 327]

An EAACI task force found out that there is a dose-response relationship for clinical efficacy as well as for immunological and safety endpoints for allergen immunotherapy. But no general dosing recommendation can be made because of variations in several aspects (e.g. reference materials and methodologies for determination of allergen content) between the studies [246].

AVAILABLE PREPARATIONS

Allergen extracts used for AIT of type I allergies are biological medicinal products [247]. There is a high complexity of the source material and the final product, since it is composed of a mixture of allergenic and nonallergenic proteins as well as other nonallergenic compounds [247, 248]. Therefore, they are manufactured by treating the allergen raw material (pollen, mites, etc.) with different extraction solutions and then removing interfering accessory substances from the enriched allergen solution by purification methods such as diafiltration (a combination of dialysis and ultrafiltration). Allergen content standardization is achieved by time- and labor-intensive in vivo and in vitro analytical methods.

Careful diagnosis may identify a few dominant sensitizing allergens which can be used for AIT [211, 238, 247]. Allergen preparations should preferably contain a single allergen or allergens from a homologous group (usually taxonomically related allergens, like *Fagales* tree pollen, grass pollen, *Oleaceae*, weed pollen, house dust mites) [212, 247, 249]. Polysensitized patients may be effectively treated with 1 or 2 separate preparations of the clinically most important allergens, which can be administered at 30-60 minute intervals at separate locations [238]. Unrelated allergens should not be mixed because of a dilutional effect or potential allergen degradation due to enzymatic activity of some allergens (e.g. mites, molds) [238, 247].

Today, standardized preparations are available with different allergen composition and different allergen processing. Fig. 13 shows the allergen extracts available.

Allergen extracts for AIT

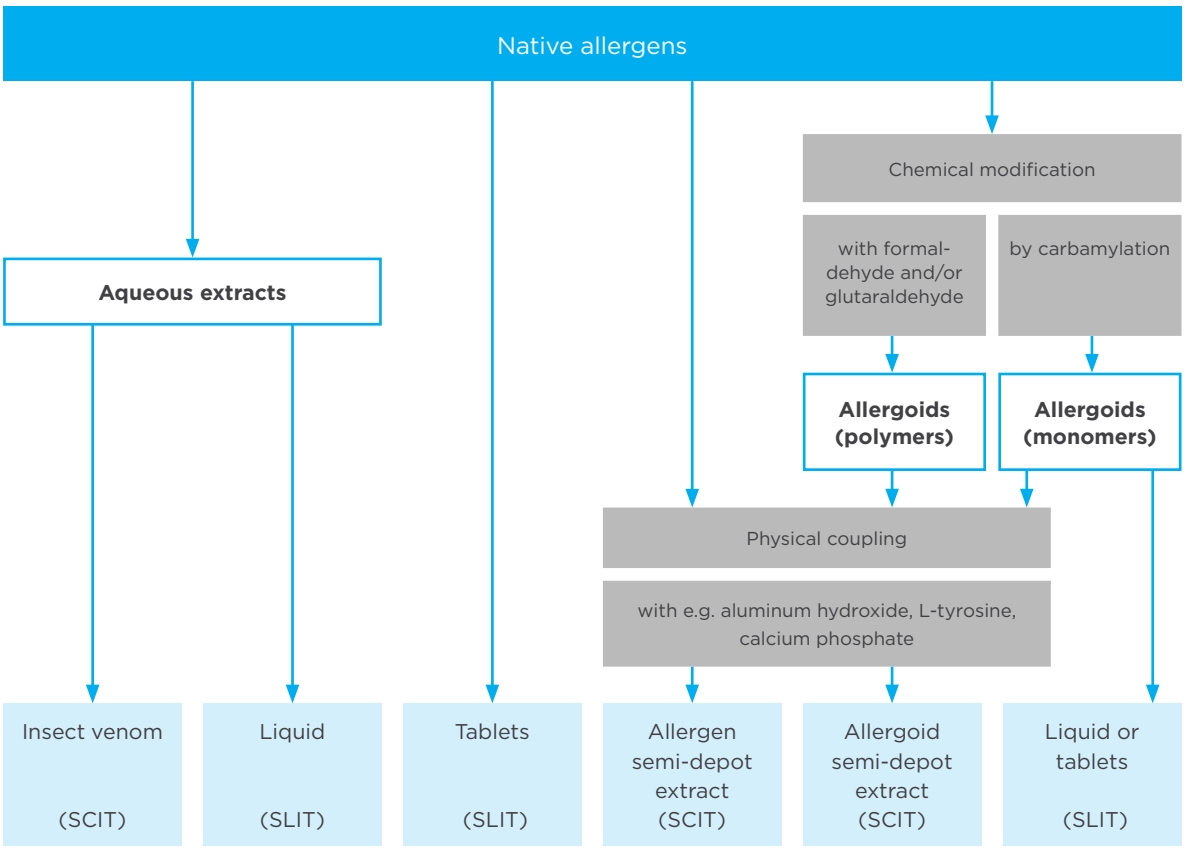


Fig. 13: Allergen extracts available for allergen immunotherapy (based on [212, 250])

Modification of allergens to allergoids

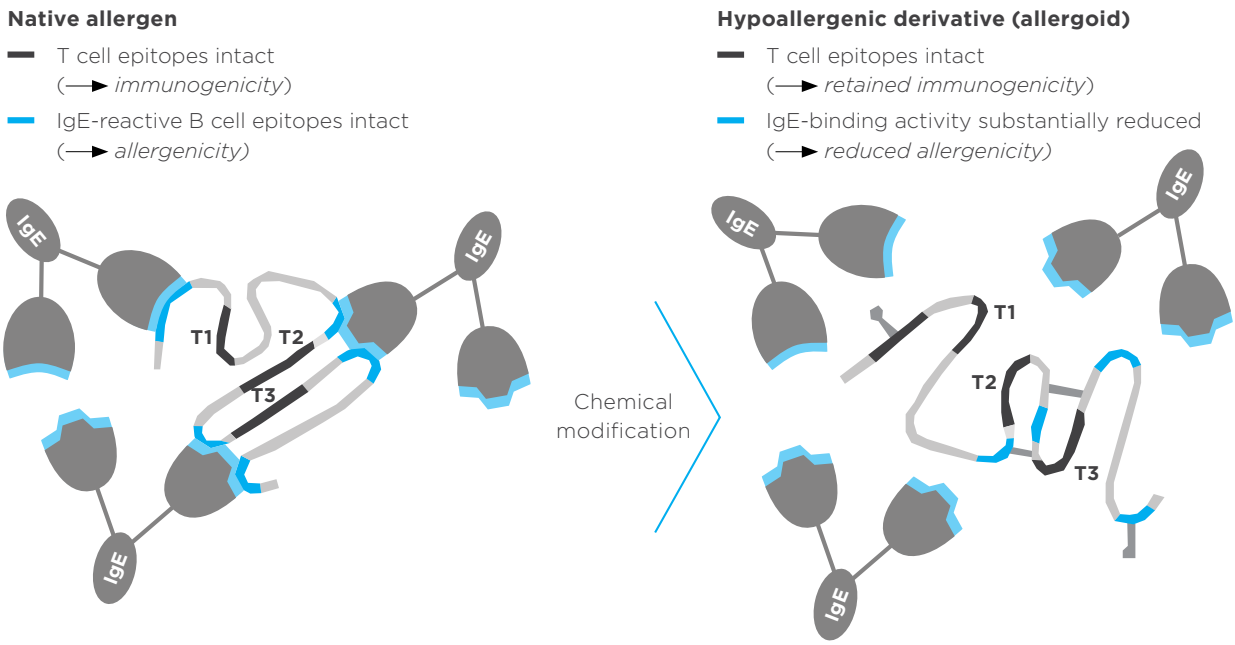


Fig. 14: Chemical modification of the native allergen to an allergoid (based on [256])

Aqueous allergen extracts or tablets, produced from the native allergen [212]
AIT originally used unchanged allergens in aqueous solutions administered to the patient by subcutaneous injections. No adjuvants were used and the allergens were not chemically modified. Aqueous allergen preparations allow more rapid allergen adsorption but are often highly potent. Meanwhile, in contrast to the USA aqueous allergen extracts are rarely used for SCIT in Europe [238] primarily in lyophilized hymenoptera venom extracts. The most SLIT preparations are aqueous solutions or tablets [238].

Physically modified products are produced by adsorption of the allergens onto carrier substances, such as aluminum hydroxide, resulting in a depot effect [212]. The depot effect produces a sustained release of the allergen from the injection site [69] whereby the injection intervals can be prolonged compared to aqueous extracts [251], resulting in a reduced number of injections [252]. Efficacy and tolerability were shown in double-blind, placebo-controlled trials for various pollen and mite preparations in allergic rhinitis and asthma [253–255] as well as for more rare allergens like *Alternaria alternata* [232].

Chemically modified products (allergoids) are produced by chemical treatment of the allergens (e.g. with formaldehyde and/or glutaraldehyde) resulting in a changed tertiary structure of the allergens. This results in a reduced allergenicity because the B cell epitopes are modified which are then hardly able to bind allergen-specific IgE-antibodies [256]. However, the T cell epitopes which are relevant for the therapeutic effect are not affected since the T helper cells bind specific amino-acid sequences irrespective of their three-dimensional structure [256]. The net result of reduced B cell epitopes and retained T cell epitopes is the reduced allergenicity with retained immunogenicity (fig. 14), enabling to increase the allergen dose without increasing the rate of side-effects [256, 257]. The development of allergoids as depot preparations finally enables a tolerable and effective SCIT with even less injections during up-dosing to reach the maintenance dose compared to unmodified depot preparations [256–260].

TOLERABILITY

"When administered correctly to properly selected patients, AIT with SCIT and SLIT preparations is safe and well tolerated". This applies to SCIT when it is performed "in a medical office/hospital with experience in this type of treatment". (212, 238)

After **SCIT** local reactions like redness, itching or swelling frequently occur at the injection site, which respond to cooling or the use of topical corticosteroids or systemic antihistamines (212, 238). Systemic reactions occur less frequently. They can range between mild to severe and affect the skin, upper and lower airways, gastrointestinal or the cardiovascular system (238). Severe, potentially life-threatening systemic reactions during SCIT are rare (212). The Paul-Ehrlich-Institute, an agency of the German Federal Ministry of Health, reported a relative frequency of severe systemic reactions after 0.0005 to 0.01 % of injections for allergoids and 0.002 % to 0.0076 % for natural extracts between 1991 and 2000 (261).

Several controlled clinical trials confirmed the tolerability of SCIT with allergoids in adults and children (262–265). A prospective longitudinal survey of AIT in local practices was conducted between September 2012 and February 2014 in France, Germany and Spain. The risk for a systemic reactions was significantly reduced during SCIT when using allergoids compared to the use of natural extracts ($p<0.001$) (266). Two open prospective post-marketing surveillance studies including approximately 5000 patients in Germany confirmed the good tolerability of pollen allergoids. After application of a total of nearly 49,000 injections no severe general adverse reaction grade 3 or 4 according to Tryba (267) was reported (268, 269).

Adverse reactions during **SLIT** are dose-dependent. Oral-mucosal symptoms are common affecting up to 70 % of patients, most of them occurring during initiation of SLIT (270). SLIT mostly is performed by the patient at home where most adverse events occur without access to immediate medical intervention in case of systemic reactions. Therefore, it is important to thoroughly inform the patients before starting SLIT especially because adverse reactions often lead to cessation of SLIT. Additionally, patients should be informed about the increased risk of adverse reactions when administration of the SLIT preparation was forgotten or when SLIT had been temporarily interrupted because of medical reasons (e.g. maxillofacial surgery, oropharyngeal lesions or infections, gastroenteritis or asthma exacerbations). (212, 238) Even though the risk for severe systemic reactions is regarded to be low during SLIT and the risk appears to be much less likely than with SCIT (212, 238), several cases of partly severe anaphylaxis during SLIT has been described meanwhile (271–276).

In case of severe adverse events during SCIT it is not recommended to switch to SLIT because there is an increased risk for potentially severe systemic reactions also with SLIT (212, 277).

A premedication with antihistamines may reduce the extent of local reactions during SCIT and SLIT but does not eliminate the possibility of systemic reactions (212, 238).

There are possible risk factors that may be related to the occurrence of systemic reactions during AIT, for example

- a high degree of sensitizations or sensitizations to several pollen species
- unstable or insufficiently controlled asthma
- previous episode of anaphylaxis
- current allergic symptoms or potential allergen exposure
- current infections, mast cell disease or hyperthyroidism
- use of β-blockers (systemic or local (e.g. eye drops))
- physical or mental stress factors (e.g. high-intensity physical exercise, sauna, excessive alcohol consumption, inadequate circulatory burden)
- inadequate up-dosing or allergen extract overdose
- during SCIT: inappropriate injection technique, e.g. intravascular application (212, 266).

INDICATIONS

The EAACI Guideline on Allergen Immunotherapy recommends [238] that AIT in allergic rhinitis with or without conjunctivitis should be considered if all of the following conditions are present

- moderate-to-severe symptoms of allergic rhinitis, with or without conjunctivitis, on exposure to clinically relevant allergen(s) which interfere with usual daily activities or sleep
- confirmation of IgE sensitization to clinically relevant allergen(s)
- inadequate control of symptoms despite symptomatic treatment and/or allergen avoidance measures and/or unacceptable side-effects of medication.

Moreover, it is recommended to use standardized products with documented clinical efficacy [238]. Patients with less severe symptoms may receive AIT when they wish to take advantage of its long-term effect on allergic rhinitis and potential to prevent asthma with grass pollen AIT [238]. In patients with coexisting asthma it should be ensured that it is controlled before starting SCIT as well as before every following injection [238]. The evidence of SCIT in children is limited to those 5 years and older [238], therefore most preparations in Europe are not recommended for children below 5 years of age.

As SCIT interferes with the immunological process of allergy, it should be administered as early as possible in the course of the disease process — before irreversible organ changes have occurred [69]. Results from controlled trials suggest that SCIT can prevent both the development of allergic bronchial asthma and further sensitizations in patients with allergic rhinitis [38, 276, 278, 279]. SCIT using hymenoptera (bee, wasp, ant) venom is indicated in children and adults experiencing systemic reactions to prevent further moderate to severe systemic sting reactions. Adults with only generalized skin reactions are also recommended to receive venom AIT as the quality of life is significantly improved in compared to carrying an epinephrine autoinjector [280].

CONTRAINDICATIONS

There are different contraindications which are relevant when performing AIT. Contraindications differed widely in recent European and national guidelines and none of them was proved by evidence-based studies. Therefore, in 2013 the EAACI created a task force to evaluate and review current literature on contraindications for AIT and to update the recommendations for AIT [281] which are as follows

Absolute contraindications

- patients aged 0 to 2 years [281]
- uncontrolled or severe asthma [238, 281]
- active forms of severe autoimmune disorders [238, 281]. Moreover, AIT should be terminated when an autoimmune disease develops [281]
- AIDS [281]
- malignant neoplasias with current disease relevance [211, 281–284]
- severe systemic reactions when performing AIT in the past [281, 283]
- starting AIT during pregnancy because an anaphylactic reaction may have life-threatening consequences for the mother and the fetus [285]; it is recommended to continue well-tolerated ongoing AIT in case of life-threatening allergies to hymenoptera venoms and it is possible to continue AIT with aeroallergens, but with caution [238, 281, 282, 286–288].

Relative contraindications

are amongst others

- patients aged 2 to 5 years [281]
- partially controlled asthma [281]
- autoimmune disease in remission [281]
- cardiovascular diseases for AIT with inhalant allergens but not for AIT with hymenoptera venom. It is recommended to evaluate together with the treating cardiologist the status of disease, the treatment and risk for anaphylaxis [281]
- primary immune deficiencies, immune defects [238]
- HIV infection. AIT may be performed in pollen-/mite-allergic patients with ‚early to middle stage' HIV disease, no AIDS-associated pathology, a CD4+ count ≥400 cells/µl and an undetectable viral load [281]
- severe mental disorders [281]
- treatment with β-blockers (topical, systemic) during AIT with inhalant allergens [38, 281, 289], because there may be an increased risk of severe systemic reactions and required treatment with epinephrine might be less effective in case of anaphylaxis [281, 290–293]
- Concomitant therapy with immunosuppressive drugs or biologicals. They can reduce efficacy of AIT. Treatment with anti-IgE is an exception [238, 294]
- insufficient patient's compliance and adherence [281].

As per the current EAACI position paper physicians' decision for or against AIT should be based on individual evaluation of any medical condition and always consider the balance of risk and benefit when performing AIT [281].

According to recent guidelines therapy with ACE-inhibitors was an absolute contraindication because single cases of severe hypotension were reported during AIT with hymenoptera venom [295, 296]. In contrast, recent trials did not confirm the increased risk of adverse reactions during venom immunotherapy [297, 298]. Respectively, today ACE-inhibitors are no longer considered to be contraindications for AIT though they may be a risk factor for more severe anaphylaxis or failure during venom immunotherapy [281, 294].

The contraindications listed above are based on the EAACI guidelines. (238, 281) Practitioners should always be aware that there may be additional or divergent contraindications for individual preparations and should always consider the respective "instructions for use and information sheet for expert" for the individual preparation.

PRACTICAL CONSIDERATIONS

The following requirements should be fulfilled in practices/clinics where it is planned to treat patients with AIT (212, 238):

Physicians
- experienced in the diagnosis and differential diagnosis of allergic rhinitis
- trained in administering AIT products
- trained in recognition and management of severe systemic events including anaphylaxis.

Personnel
- trained in treating severe systemic events.

Practice
- facilities for observing patients for at least 30 minutes after AIT
- availability of an equipment for treating adverse events.

Patients should be informed about
- practicalities of AIT
- expected benefits
- potential adverse events and the management
- possible alternatives.

In patients with allergic rhinoconjunctivitis, AIT should be performed for at least 3 years (212, 238, 299) to achieve long-term efficacy after treatment discontinuation (238). AIT may be individually prolonged if there are residual symptoms or when dose reduction was necessary. Efficacy of AIT depends on the cumulative allergen dose (4). If there is no improvement after one and not later than 2 years, diagnosis and indication should be critically checked. In single cases it is reasonable to change the preparation or to switch from preseasonal to perennial pollen AIT. But stopping AIT is an option, too. (212)

SUBLINGUAL IMMUNOTHERAPY (SLIT)

SLIT involves holding the allergen extract under the tongue for some time and then swallowing it. Dose escalation for many SLIT products is performed under medical supervision, the patient should be observed for at least 30 minutes afterwards (238). The further treatment is performed by the patients themselves at home. Since the most adverse events develop at home without any medical observation, it is important that the patient has clear, simple instructions on how to recognize and behave in case of adverse events (212).

SLIT is regarded to be well tolerated. Severe systemic reactions seem to occur less often than with SCIT although the safety profile is comparable for SCIT and SLIT (300). Nevertheless, anaphylactic reactions to SLIT have been reported (246, 271, 272, 276, 277, 301–306).

The first preparations to be used for SLIT were liquid preparations but SLIT tablets are now available as well.

As to the current EAACI position paper SLIT is generally recommended for children and adults suffering from seasonal allergic rhinoconjunctivitis (238). The recommendation is of highest level (evidence level I (based on systematic reviews, meta-analysis, randomized controlled trials), grade of recommendation A (based on level I studies)) for
- adults and children with seasonal allergic rhinoconjunctivitis treated pre-/coseasonally to achieve clinical benefit during SLIT
- adults and children with seasonal allergic rhinoconjunctivitis treated perennially to achieve clinical benefit during SLIT
- children with seasonal allergic rhinoconjunctivitis treated with aqueous solutions to achieve benefit during SLIT
- adults and children with seasonal allergic rhinoconjunctivitis treated with grass pollen tablets to achieve clinical benefit during SLIT
- adults and children with seasonal allergic rhinoconjunctivitis treated with grass pollen tablets or solutions perennially to achieve benefit for at least one year after cessation of AIT
- adults and children with perennial allergic rhinoconjunctivitis when using mite tablets to achieve benefit during SLIT.

Meta-analyses, systematic reviews and respective overviews confirmed efficacy of SLIT in allergic rhinoconjunctivitis and allergic asthma (300, 307–309).

SUBCUTANEOUS IMMUNOTHERAPY (SCIT)

SCIT generally consists of an initial treatment phase during which the allergen dose is increased from injection to injection, and a maintenance phase during which a constant allergen dose is administered at longer time intervals. Generally, up-dosing during SCIT using modified and unmodified allergen extracts is performed in 1 to 2 weeks intervals. With cluster or rush regimens it is possible to administer 2 to 3 injections per treatment day, followed by a one-week break [69]. Meanwhile, to increase patients' compliance shortened up-dosing regimens for grass pollen allergoids with only 3 weekly injections are available which are comparably safe and tolerable like conventional up-dosing with 7 injections [310, 311].

Usually, the allergen extracts are administered by subcutaneous injections into a lifted skin fold a hand's width above the olecranon on the extensor side of the upper arm [212].

Treatment should be started when the patient is asymptomatic or almost asymptomatic. AIT in patients with allergies to perennial allergens such as mites should be started when allergen exposure is lowest and avoidance measures are in place [238]. In patients with seasonal airway allergies, preseasonal treatment is usually sufficient to reach significant efficacy [265, 312, 313]. Moreover, SCIT using pollen allergens may also be administered perennially in patients, using a reduced dose during the respective pollen season. A randomized, double-blind, comparative trial showed that perennial SCIT using a 6-grass pollen allergoid was significantly more effective compared to preseasonal SCIT after 3 years [314]. Moreover, SCIT was significantly more effective compared to baseline already in the first grass pollen season with increasing effects in the 2nd and 3rd year irrespective whether it was administered preseasonally or perennially [314].

As to the current EAACI position paper SCIT is generally recommended for children and adults with moderate to severe allergic rhinoconjunctivitis that is suboptimally controlled with symptomatic treatment. The recommendation is of highest level (evidence level I), grade of recommendation A for

- adults with moderate to severe seasonal allergic rhinoconjunctivitis when administered perennially to achieve clinical benefit during SCIT
- adults with seasonal allergic rhinoconjunctivitis irrespective whether administered pre- or pre-co-seasonally to achieve clinical benefit during SCIT
- adults with seasonal allergic rhinoconjunctivitis when grass pollen are administered perennially to achieve clinical benefit during AIT and for at least one year after cessation of SCIT
- adults with seasonal and perennial allergic rhinoconjunctivitis induced by pollen or house dust mite when using modified (allergoids) and unmodified allergen extracts to achieve clinical benefit during SCIT. [238]

Efficacy of SCIT is confirmed by various double-blind, placebo-controlled trials which have demonstrated clinically relevant effects on symptoms and reduction in the use of symptomatic medication during the first treatment year, in the 2nd and 3rd treatment period as well as in post-treatment years [40, 300]. This is confirmed by meta-analyses and systematic reviews showing efficacy and safety in seasonal allergic rhinitis/rhinoconjunctivitis [253, 300], house dust mite-allergic rhinitis [315] and allergic asthma [254, 308, 309].

SCIT might have a disease-modifying capacity and prevent the progression from rhinitis to asthma [40, 238].

There are evidence-based recommendations for the use of SCIT with hymenoptera venom for patients with large local reactions and severe systemic reactions. The only treatment that has the capacity to prevent further systemic reactions is venom immunotherapy (VIT). VIT is reported to be effective in 77 % to 84 % of patients treated with honeybee venom, and in 91 % to 96 % of patients treated with vespid venom. [280]

SCIT with allergoids was shown to be effective and tolerable in subjects suffering from grass, birch pollen or house dust mite-allergic rhinoconjunctivitis with or without asthma in randomized, double-blind, placebo-controlled trials for the 1st and 2nd treatment year [262, 265, 312, 316, 317]. Efficacy increases in the 2nd treatment year [265] and there are hints of sustained efficacy in the 3rd treatment year [265, 318] and of long-term efficacy for up to 6 years in adults [319, 320] and 12 years in children after terminating a 3-year grass pollen SCIT [278, 321]. "Children with house dust mite-induced allergic asthma benefit from SCIT with a hypoallergenic mite extract that allowed a strong steroid-sparing effect while maintaining guideline-defined asthma control" [263]. As to the EAACI position paper "SCIT is a safe and well-tolerated treatment when the injections are given in a medical setting by experienced personnel trained in the early recognition of systemic reactions and how to manage them". [238] Allergoids are associated with a significantly reduced risk to cause systemic adverse events compared to unmodified extracts. [238, 266, 322]

Effectiveness and tolerability of SCIT with pollen allergoids in daily practice was confirmed by post-marketing surveillance studies [268, 269] and real-world data [323, 324].

INCREASING EFFICACY OF AIT

Several parameters may increase the effect of AIT with inhalant allergens, for example [212, 238]

- allergen extracts from a single allergen species or a mixture of homologous allergens from the same biological family for patients with allergy to grass pollen, tree pollen and house dust mites
- short duration of allergic disease
- minor involvement of the lower airways
- young age (but not before the age of 5 years)
- high cumulative AIT dose
- allergen extracts of high quality
- good patient's compliance and adherence.

Since AIT is recommended to be performed for at least 3 years, patient's compliance and adherence plays an important role to achieve optimal efficacy and long-term effects. Stopping AIT prematurely and/or taking or administering the allergen extract less frequently than recommended by the manufacturer may clearly reduce the effect of AIT [212]. Patient's adherence for SLIT seems to be lower than for SCIT [325-327].

BENEFITS OF AIT

AIT is effective in

- **IgE-mediated allergic rhinitis, rhinoconjunctivitis with or without asthma** in children and adults. Randomized, double-blind, placebo-controlled trials showed a reduction of allergic symptoms as well as reduced need of antiallergic medication [253, 254, 265, 307, 316, 328–333]
- **mild to moderate allergic asthma** by improving symptom and medication scores in children and adults [309, 334]. AIT can improve measures of bronchial hyperreactivity [309]. Moreover, there are hints that AIT can reduce the need of inhaled corticosteroid while maintaining asthma control in children suffering from mild to moderate house-dust mite allergic asthma [263]
- **hymenoptera venom allergy** since VIT is the only treatment that can potentially prevent further systemic sting reactions [280].

AIT has

- **long-term effects in children and adolescents with pollen-allergic rhinitis** because the treatment effect may persist also after cessation of AIT [278, 279, 299, 321, 335–337]
- **preventive effects** because it may protect patients with allergic rhinitis from developing asthma [40, 212, 238, 337]
- **preventive effects** since it may prevent the development of new sensitizations [278, 320, 321, 338–341].

AIT can

- **improve patients' quality of life** in allergic rhinoconjunctivitis [69, 320].

AIT is

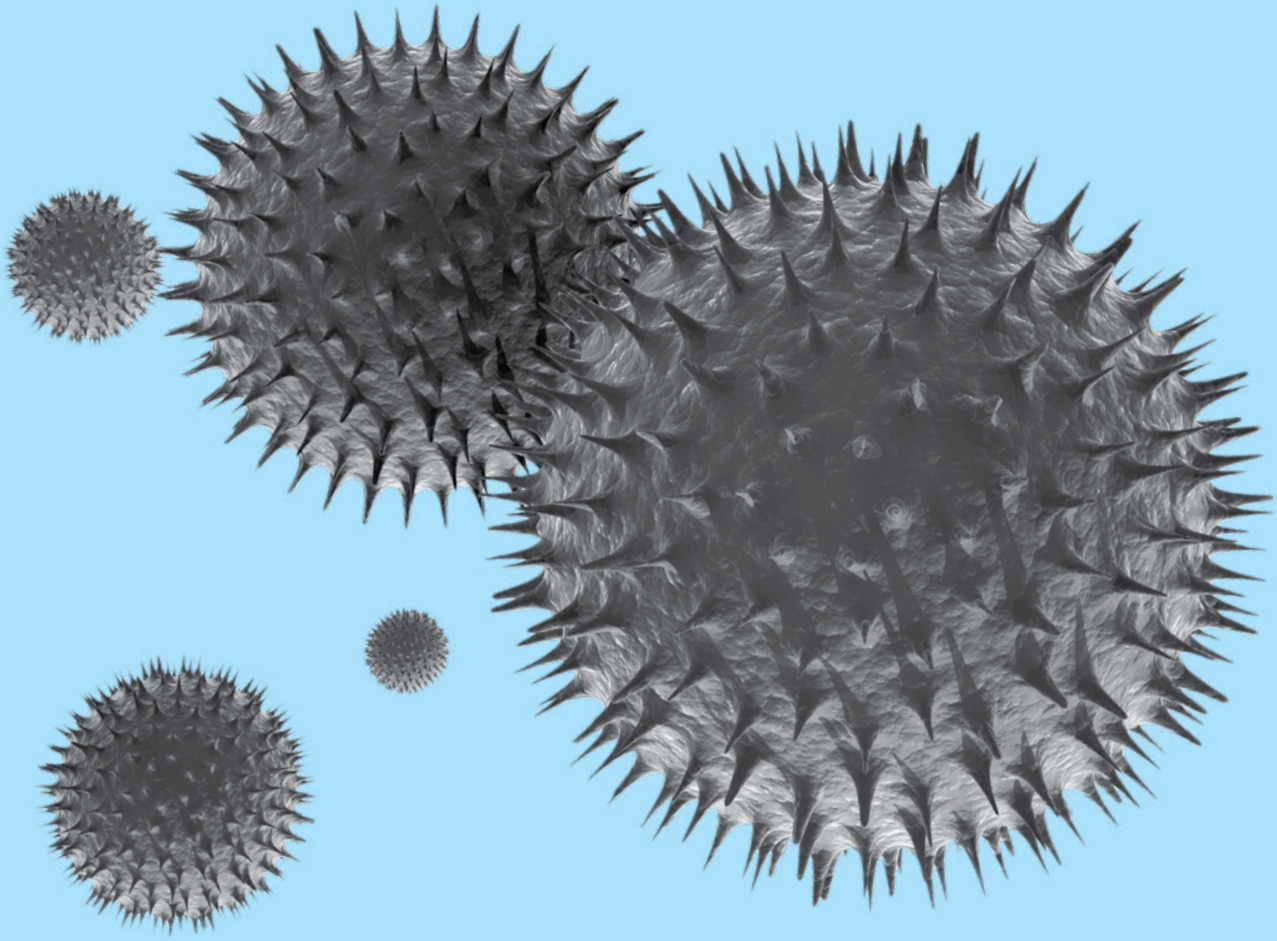
- **well tolerable**, when the preparations are appropriately administered to patients selected based on the indications for AIT [69, 212, 238, 265, 300, 316, 342–345]
- **more cost-effective than symptomatic treatment** in allergic rhinitis and allergic asthma in the long-run [346-349].

The information mentioned above reflect the current recommendations of the EAACI guidelines. This applies particularly to the (contra-) indications for AIT. During application, the information provided by the respective manufacturer should always be given priority over the methods presented here! They are approved by the local authorities and are mandatory concerning the product-specific information!

In allergic patients, the administration of high allergen doses activates T regulatory cells which lessen the allergic Th2 cell predominance and, in the long term, achieve a Th1/Th2 immune balance similar to that in healthy individuals. Above all, successful AIT requires the use of high allergen doses over a treatment period of at least 3 years.

Efficacy and tolerability of AIT has been shown in several clinical trials for allergic rhino-conjunctivitis with or without allergic asthma. In seasonal allergic rhinitis SCIT is as least as effective as symptomatic treatment already as early as the first pollen season. The major difference to symptomatic treatment is that AIT has effects that also persist after cessation. Moreover, AIT has preventive effects and can protect the patients from developing asthma from allergic rhinitis as well as the development of new sensitizations.

APPENDIX



Scanning electron microscope picture of pollen

LIST OF ABBREVIATIONS & ACRONYMS

4PR	4-Phase Rhinomanometry
AAR	Active Anterior Rhinomanometry
ACE	Angiotensin Converting Enzyme
AcRh	Acoustic Rhinomanometry
AIT	Allergen Immunotherapy
ARIA	Allergic Rhinitis and its Impact on Asthma
Bet v 1	Major allergen of birch pollen *(Betula vulgaris)*
BPT	Bronchial Provocation Test
Breg	B regulatory cell
CAS-2	cross-sectional area 2
CD4	Cluster of Differentiation 4 or Cluster of Designation 4 or Classification Determinant 4
CPT	Conjunctival Provocation Test
DGAKI	German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie)
EAACI	European Academy of Allergy and Clinical Immunology
EFA	European Federation of Allergy and Airways Diseases Patients' Associations
ELISA	Enzyme-linked Immunosorbent Assay
ENT	Ears, Nose and Throat
EU	European Union
Fc	Fragment crystallizable
FcεR	Fcε receptor
FEV1	Forced Expiratory Volume in one second
Fig.	Figure
GA^{2}LEN	Global Allergy and Asthma European Network
GINA	Global Initiative for Asthma
HIV	Human Immunodeficiency Virus
IAR	Intermittent Allergic Rhinitis
ICT	Intracutaneous Test
Ig	Immunoglobulin
IL	Interleukin
kU/L	Kilounits/liter
LABA	Long-acting β_2-agonists
MHC	Major Histocompatibility Complex
mod. acc.	modified according
NaCl	Sodium chloride
NPT	Nasal Provocation Test
PAR	Persistent Allergic Rhinitis
PNIF	Peak Nasal Inspiratory Flow
RSV	Respiratory Syncytial Virus
SABA	Short-acting β_2-agonists
SCIT	Subcutaneous Immunotherapy
sIgE	Specific IgE
SLIT	Sublingual Immunotherapy
SPT	Skin Prick Test
Tab.	Table
Treg	T regulatory cell
TGF	Transforming Growth Factor
Th	T helper cell
TNF	Tumor Necrosis Factor
TNSS	Total Nasal Symptom Score
VAS	Visual Analog Scale
WAO	World Allergy Organization
Yr	year

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