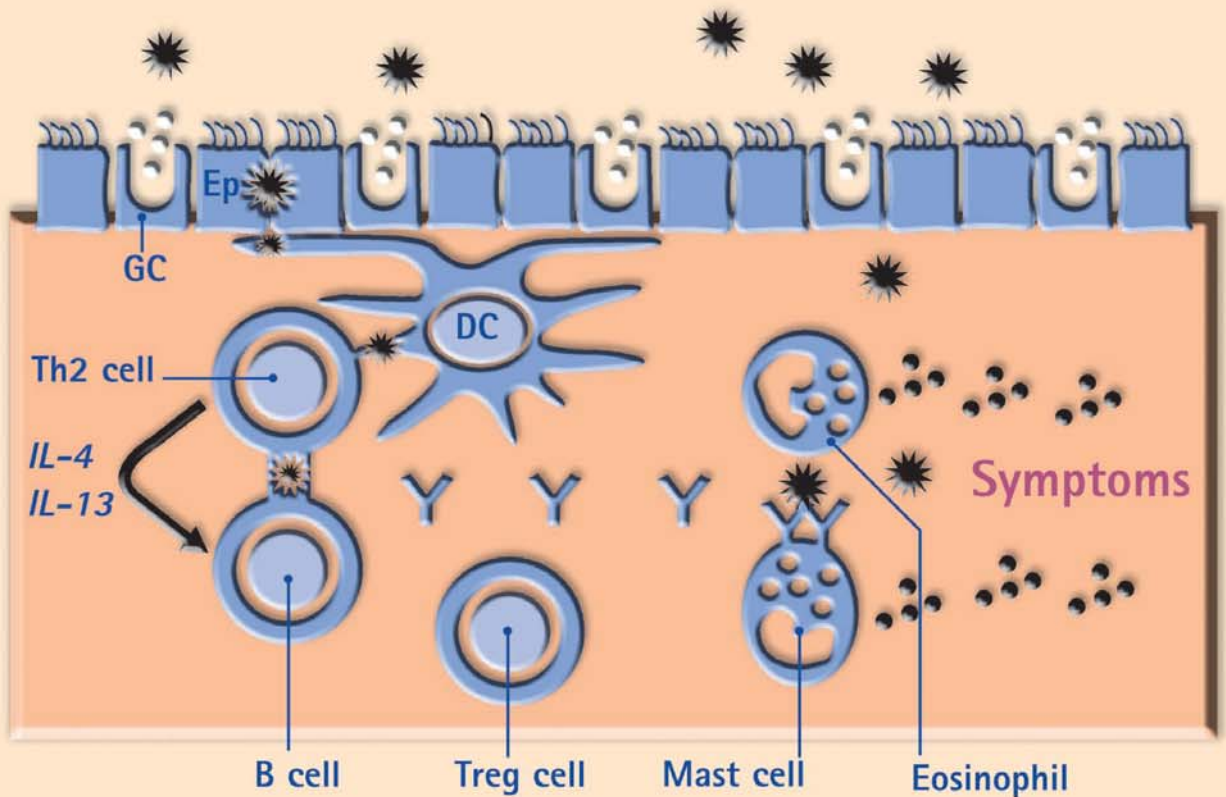


MANAGING ALLERGY

A. CUSTOVIC and T. A. E. PLATTS-MILLS



C L I N I C A L P U B L I S H I N G

Managing Allergy

EDITED BY

A CUSTOVIC, TAE PLATTS-MILLS

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PART I

Diagnosis

IgE antibody tests in diagnosing allergy

STAFFAN AHLSTEDT, LEN FROMER, LARS SODERSTROM

KEY POINTS

- 1.** Without firm diagnosis, conditions with allergic aetiology are difficult to distinguish from conditions with different aetiology.
- 2.** Sensitization and presence of IgE antibodies is not a dichotomous, 'yes/no' but rather a quantitative phenomenon that needs to be interpreted in the context of the case history.
- 3.** The presence of risk factors increases the risk of allergy as a contributing factor to symptoms, and this is multiplied by the presence of IgE antibodies and exposure to the allergens.
- 4.** Exposure to different allergens in the sensitized individual works in concert. This can be emphasized even more by immunological cross-reactivity between different allergen components.
- 5.** The sum of IgE antibodies quantitatively demonstrate:
 - a. the risk of current allergy and
 - b. risk of reaction and exacerbation,
 - c. aggravating the effect by confounding factors as well as
 - d. the allergy evolving over time.
- 6.** Decreasing IgE antibody levels can demonstrate development of tolerance and out-growth of the allergy.

Introduction

Diagnostic testing is used to provide evidence for an allergic as distinct from a non-allergic aetiology, to establish the degree of atopy, and to identify the offending allergen/s. Since allergic diseases generally present as a multitude of symptoms and signs and since they tend to evolve over time, the conditions are often difficult to differentiate from similar clinical conditions that are non-allergic in origin. Thus, as many as 60–70% of conditions commonly suspected as allergic may have a different aetiology [1]. For example, respiratory symptoms that resemble allergy

presenting seasonally or perennially, may actually be due to infections, vasomotor reflexes, anatomical conditions [2], or chronic obstructive pulmonary disease. Furthermore reactions elicited by foods may give identical signs regardless of being of allergic or non-allergic nature i.e. lactase or diamino oxidase insufficiency [3,4]. To date there are no prospective studies that have specifically aimed to differentiate between allergic and non-allergic reactions in the respiratory tract on the basis of clinical symptoms, signs, and physical examination. Attempts have been made to distinguish between different aetiologies for food reactions, especially those of the anaphylactic type [5]. This chapter presents information regarding how case history and physical examination provide a certain level of diagnostic information and how this level can be elevated and improved upon when combined with accurate and objective diagnostic tests. In reaching the diagnosis the time and costs for diagnostic procedures need to be considered in the context of patient management and utilization of the resources of the healthcare system. This also relates to the formulated goals of the healthcare system as characterized by safety, effectiveness, timeliness, patient focus, cost and efficiency [6].

Definitions

It is essential to define the terms used when discussing allergic disease. The definitions of several key terms are given in Box 1.1 (from [7]).

Box 1.1

- **Total and specific IgE:** total IgE (tIgE) means the total amount of the immunoglobulin IgE present in blood, irrespective of what these IgE molecules may bind to; specific IgE means specific IgE (sIgE) antibodies binding to particular and identifiable allergens.
- **Sensitization** means that sIgE antibodies have been formed due to previous allergen exposure, as evidenced by blood or skin tests.
- **Atopy** is the propensity to produce specific IgE (sIgE) antibodies upon exposure to common allergens in the environment.
- **An allergic reaction** is an immunologically-determined clinical reaction to an identified substance or allergen. **IgE-mediated allergy** means that the immunological mechanism is related to sIgE.
- **Clinical sensitivity and specificity:** **sensitivity** is defined as the ability of a test to identify patients with the condition; **specificity** defines the ability of the test to correctly exclude those who do not have the condition.

What to accomplish by setting the diagnosis

There are well-documented genetic–environmental interactions between sensitization and the development of disease as well as other contributing factors in the expression of the disease. For example, 40% of young children with atopic dermatitis have been shown to develop asthma later in life [8]. In such a context, to be able to provide the best care for the patient, the diagnostic information should

Box 1.2 Goals to be accomplished with a diagnostic work-up.

Diagnosis

- Distinguish allergy vs non-allergy
- Identify allergen(s) which may be involved

Risk patient prediction

- Confounding factors
 - Virus infection
 - Exposure to environmental factors
 - Other allergies e.g. food, drug

Disease course prediction

- Transient vs persistent disease
- One symptom followed by other symptoms: Allergy March
- Sensitization as a prognostic parameter to predict upcoming allergic disease
 - Early vs late
 - Mono vs multi
- Natural course of allergic disease: food allergy and wheeze/asthma

Treatment prediction

- Responsiveness to pharmacotherapy
- Avoidance strategies:
 - inhalants
 - food diets
 - combinations between avoidance and pharmacotherapy to lower the medication burden

Outcome of specific immunotherapy

also include prognostic information for evaluation of the disease process and possibly also prediction of the outcome of treatment. Examples of accomplishments with any diagnostic work-up should cover the aspects listed in Box 1.2.

Establishing an allergy diagnosis

Considering the difficulties in distinguishing between allergic symptoms and those symptoms that are non-allergic in origin (or both), and to accomplish the diagnostic goals, as a first step any practising physician needs to consider several important questions:

1. Is allergy contributing to the presence of symptoms (e.g. wheeze, rhinitis, eczema)?
2. Is allergy contributing to the severity and frequency of the symptoms?
3. Will the symptoms become continuous or persistent or resolve?

Information about the family history of allergic disease and the individual's own possible other allergic diseases may help in this decision-making process. Particular and pertinent questions to ask the patient and evaluate in the environmental context would include:

1. Do your symptoms get worse when in contact with dust and during cleaning the house, or when you're in contact with cats, dogs, pollens, or in environments with mould?
2. Are symptoms worse during any particular time of the year? Have you had symptoms during the last 12 months?
3. Are your problems associated with your eyes, nose, lungs, stomach or skin?
4. Have you had hay fever? Have you been tested for allergy before and were the tests positive; and has a doctor already diagnosed you with rhinitis or asthma?
5. Do other substances like tobacco smoke, or odours from flowers and perfume, increase your problems?
6. Does anybody in your family suffer from asthma, hay fever or eczema?

In addition to those questions, more recent publications suggest that information regarding obesity, physical inactivity and time spent indoors may add to the precision of the diagnosis [9,10]. The importance of a thorough case history can be illustrated from several epidemiological studies. They have addressed some of the questions and related them to an increased risk if the factor is present, usually expressed as odds ratio (OR). The OR represents a measure of whether the probability of a certain event or disease is the same (OR = 1) or different (OR higher or lower than 1) for individuals from two different populations. Box 1.3 gives some examples of approximate risk as published in the literature if a certain factor is present.

Box 1.3 Risk factors found in several studies on children. Odds ratios approximated from the literature [11–15].

In relation to persistent wheeze

Male gender?	OR = 2
Did the child wheeze before 3 years of age?	OR = 3
Does mother have asthma?	OR = 4
Does any parent have asthma?	OR = 3
Did mother smoke during pregnancy?	OR = 2
Was there eczema before 2 years of age?	OR = 2

In relation to persistent eczema

Is there a parental allergy?	
This is atopic eczema	OR = 2
Will this eczema stay and get worse until school age?	
Frequent scratching	OR = 6
More than 2 allergic family members	OR = 2
Having early wheeze	OR = 2

Thus, asking simple questions can raise suspicions as to what the aetiology of the symptoms may be. However, although contributing to the diagnosis, case history and physical examination are on their own not sufficient to diagnose the presence and extent of allergy. This is especially true in patients with rhini-

tis, asthma and/or atopic dermatitis, and stinging insect anaphylaxis. Such cases require confirmation of the presence of a sIgE-mediated aetiology [16,17].

Information on the IgE system

The level of total IgE (tIgE) is a function of the genetic control of IgE production and the synthesis of specific IgE antibodies (sIgE). Total IgE levels can be elevated in a number of non-allergic conditions such as parasite infestation, ataxia telangiectasia, etc. In atopic dermatitis, tIgE levels have some—albeit weak—relation to the severity of atopy. They are also to some extent associated with the severity of allergy in asthma/rhinitis. However, the tIgE values in normal and atopic individuals vary with age and selection of the reference population [18]. Thus, there is a considerable overlap between non-atopic and atopic patients, and also between the different allergic diseases, making the interpretation of the total IgE levels in an individual patient of uncertain value. Further, the tIgE levels do not reveal much information regarding the progress of allergic disease. tIgE is not a good marker for screening to identify atopic individuals, although high tIgE levels suggest the need for further investigation. In contrast, sIgE are specifically produced following exposure of a susceptible individual to an allergen. sIgE levels reflect exposure to the offending allergen/s and more importantly the clinical reactivity of a given patient. Allergen-specific IgE molecules are present on mast cells in the skin and other organs as well as in blood. They bind to these cells in these tissues and can thereby initiate a clinical reaction upon subsequent allergen exposure. Thus, the presence, quantity, and specificity of sIgE can be regarded as a risk factor for clinical allergy in the respiratory tract, skin, and gastrointestinal tract, upon exposure to the allergen.

The diagnostic performance of a test for specific IgE antibodies—i.e. its ability to detect an allergic aetiology—is usually expressed as its clinical sensitivity and specificity using an arbitrarily chosen cut-off value as compared to the actual diagnosis. Good sensitivity and specificity results for IgE antibody tests compared both with doctor's diagnosis and with skin prick testing (SPT) have been documented for a variety of allergens using different methodologies [19]. However, in this context it is important to realize that there is an uncertainty in the determination of sIgE antibodies with SPT as well as in the doctor's conclusion [20]. Data for the best documented system include clinical and serological information for thousands of patients in more than 3 000 peer-reviewed publications. For this system, values above 90% sensitivity, specificity, and positive predictive value have been demonstrated [21]. Similar documentation for other systems is less clear but they frequently compare their analytical performance with ImmunoCAP [22–24].

There is a considerable documentation that information on the presence of sIgE antibodies from a well-established assay system adds significantly to the precision of the diagnostic work-up. In more general terms, for a variety of reasons, studies have shown that when clinicians use only the history and physical examination, the accuracy of their diagnoses rarely exceeds 50% [20]. Box 1.4 gives

some examples from the literature of approximate increase of risk if a specific factor is present in conjunction with sIgE antibodies.

Box 1.4 Risk factors to consider in the diagnosis of a child with symptoms of wheezing [11–15].

	Signs at 2 years of age	IgE antibodies also at 7 years of age
Does mother have asthma?	OR = 4	OR = 16
Was there eczema before 2 years of age?	OR = 2	OR = 10
Was there eczema and sensitization before 2 years of age?	OR = 7	
Was there sIgE to inhalants before 2 years of age?	OR = 3	OR = 10
to foods and inhalants?	OR = 9	

Diagnosis of a child with eczema

Is there a parental allergy?	
Risk for atopic eczema	OR = 2
Are there sIgE antibodies?	
Risk for severe atopic eczema	OR = 3
Having sIgE antibodies before 12 months of age is worse than at 24 months of age	
Will eczema stay and get worse until school age?	
Presence of sIgE antibodies	
To food	OR = 3
Wheat	OR = 7
Soy	OR = 5
Inhalant	OR = 2
Any	OR = 3

Dose–response relationship between exposure to allergens and formation of sIgE

It is important to emphasize that development of allergy and formation of sIgE is a cumulative process. Therefore, it should not be regarded as an ‘all or nothing’ phenomenon. Instead, all individuals (even if they are sensitized) have a certain level of tolerance to exposure to offending substances. However, when such exposure to the offending substance is increased, symptoms may become evident. In this context, it is also important to understand that several allergens may have components with similar structures, i.e. they are cross-reactive and they can induce sIgE antibodies and elicit clinical reactions. As a consequence, the individual allergen load may be higher than that which appears immediately obvious. Thus, birch, alder and hazel contain similar structures, as do different grasses. Furthermore, pollen allergy may manifest as a clinical reaction to certain vegetables due to structural similarity of some of the molecules of the food compared

with the pollen [25–27]. The risk of such clinical reactions to food has been estimated and is indicated in Box 1.5 [28].

Box 1.5 Estimated risks of clinical reaction to cross-reacting allergens if allergy is present to one allergen as verified by double-blind placebo-controlled food challenge [28].

If allergic to	Risk of reaction also to	Estimated risk
Pollen	Fruits/vegetables	55%
birch, ragweed	apple, peach, honeydew	
A legume	Other legumes	37%
like peanut	peas, lentils, beans	
A grain	Other grains	20%
wheat	barley, rye	
Peach	Other Rosaceae	55%
	apple, plum, cherry, pear	
A tree nut	Other tree nuts	37%
walnut	brazil, cashew, hazelnut	
Melon	Other fruits	92%
	watermelon, banana, avocado	
A shellfish	Other shellfish	75%
shrimp	crab, lobster	
Cow's milk	Beef	10%
	hamburger	
Latex	Fruits	35%
	kiwi, banana, avocado	

There is a close link between allergy to birch, alder and hazel pollen, and oral allergy to hazelnut, apple, pear, stone fruits, tomato and almond. Similarly, mugwort exhibits cross-reactivity with celery, carrot and certain spices. More information has demonstrated a relationship between grasses and legumes while grass pollen has also been associated with reactions to tomato and peas, including peanut and wheat, and also melon, watermelon and orange, whereas ragweed is associated with melon and banana. There are also well-documented common structures between arthropods like mite and shellfish, and between latex, banana, kiwi and avocado. In such cases, the different allergens can work in concert adding to the relative amount of similar structures presented to the individual, which can increase production of sIgE levels reactive to the allergen in question. For further information on cross-reactivity the reader is referred to [25–28].

In a multi-sensitized individual, the sum of the individual sIgE antibody levels and the consequences of multiple allergen exposures may be functionally additive or synergistic in activating the inflammatory processes leading to symptoms [29]. In addition, the extent of exposure to a given allergen may be an important factor in producing symptoms. When it is practical, avoiding allergen exposure for sensitive individuals is a useful tool in the management of the patient. It has been shown that children with dust mite allergy who have symptoms at sea level where

dust mite exposure is high improve clinically by moving to higher altitudes where dust mites are not present [30]. In contrast, there has been a recent debate as to whether very high exposure to an allergen can actually decrease clinical reactivity and permit development of tolerance in the patient and induce protection of the allergic subject [31,32]. In fact, heavy exposure to allergen, particularly from pets (such as cats and dogs), may preferentially drive other immune responses rather than sIgE formation, and therefore result in less allergy [32,33]. This emphasizes the need to understand both the qualitative and quantitative extent of relevant exposures in the investigation of the patient.

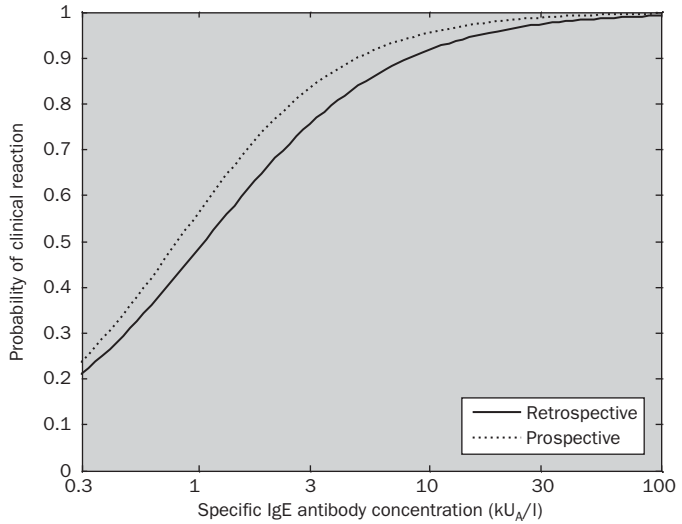
Using sIgE results for risk assessment in patients with allergy

A higher level of exposure to allergens generally results in corresponding sensitization and formation of specific IgE antibodies to those allergens. Consequently, by utilizing a quantitative approach to the IgE antibody results, rather than a dichotomous 'yes/no' approach, recent studies suggest that for the individual patient, even higher precision can be achieved. This was first demonstrated in food allergy by Sampson and his colleagues [34,35]. In those studies, a higher sIgE antibody value implies that the subject has a substantial risk of reacting with symptoms upon exposure and the patient can be diagnosed without further measures. In contrast, a lower, albeit 'positive', value may not be completely predictive of whether or not the subject will exhibit a clinical reaction upon exposure. In these cases a referral to an allergist for a challenge procedure should be considered. A still lower value implies a rather low probability that the subject will react upon exposure. Consequently, the food may not be considered as a likely problem for symptoms (Fig. 1.1). Despite this, in cases with a convincing history despite a low sIgE value, further investigation may be necessary. Factors to consider are that the levels depend on age and that different food allergens vary in their potency and show different values for when a clinical reaction is likely to occur [36–39] (Fig. 1.1). Thus, it is necessary for the physician to get a feeling for the probability related to the allergy in question. For this reason, for patients with food allergy it may be appropriate to consider referral to an allergist. In this context it must be emphasized that other reactions to food like gliadin in coeliac disease, lactose in lactase deficiency, histamine in histamine-containing foods also need to be considered in relation to the case history and these are not associated with IgE antibody results.

For inhalant allergy, implementing sIgE antibody testing may increase the accuracy of the diagnosis and the management of the patient to a considerable extent. In particular, with this knowledge, a number of uncertain and equivocal cases can be given a firm diagnosis [40,41].

Quantitative sIgE antibody patterns and symptom induction similar to those described for food allergy have been revealed for a variety of allergens, providing information on the extent to which allergy contributes to the expression of symptoms

Fig. 1.1 Probability curves for whether a patient will have a reaction when ingesting hen's egg in relation to the levels of sIgE antibodies. With permission from the American Academy of Allergy, Asthma and Immunology [34,35].



[20,33,42]. Since most allergic individuals exhibiting symptoms have sIgE to several allergens and rarely only to one, quantitative sIgE evaluation may reveal the relative importance of the different offending allergens. Thus, reports from a prospective birth cohort study demonstrate that a single positive sIgE test was seldom on its own associated with clinical allergic disease. In contrast, in that study, when there were four or more positive sIgE tests out of a total of 14 common allergens, or a sum of the individual sIgE antibody levels above $34\text{kU}_A/\text{l}$ to these allergens, there was a 75% likelihood of identifying those individuals with allergic disease [43]. In practical terms, this implies that to obtain an adequate diagnosis, allergy tests should be performed to the most common allergens evident in the patient's environment, and that quantitative information should be gained and evaluated both for individual allergens and summated (see below and Fig. 1.2).

Recent information also demonstrates that the sum of sIgE antibody levels against the most common inhalant allergens in the environment of the individual can answer whether allergy contributes to the clinical expression of wheeze in preschool children (Box 1.6) [33]. In fact, with increasing levels of sIgE antibodies, the risk of having current or persistent wheeze and impaired lung function in children increases. As an example, $10\text{kU}_A/\text{l}$ of sIgE to the allergens of cat, dog and mite summed, corresponds to a three-fold increase in the risk of symptomatic wheeze compared to those without such sIgE, and $30\text{kU}_A/\text{l}$ a four-fold increase in risk (Fig. 1.2). In contrast, tIgE does not provide such information. Using quantitative sIgE results in such a way needs well-standardized methods. Evaluation of the size of the skin prick test weal may also give similar information provided that the testing and interpretation is carefully standardized. Such standardization and evaluation of the procedure has to be done in each clinical setting and may be difficult in clinical routine practice. In practical terms, the available information implies that patients with allergic asthma should be investigated by measuring their

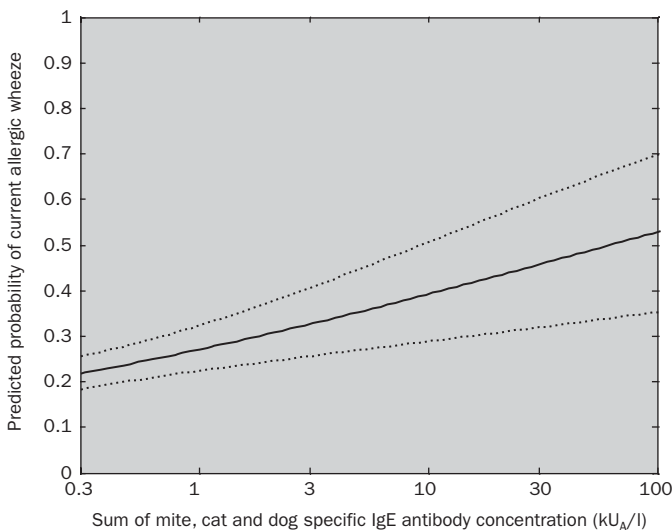


Fig. 1.2 Probability that a reaction of wheeze in a 5-year-old child is of allergic nature in relation to sIgE antibodies to mite, cat and dog. The 95% percentile is given. With permission from the American Academy of Allergy, Asthma and Immunology [33].

sIgE antibody levels to the most prominent allergens in their environment. Such measures will allow the optimization of pharmacotherapy along with attempts to decrease the allergen exposure. On the contrary, a low or negative sIgE antibody level indicates the need to consider an alternative ‘non-allergy’ treatment.

Box 1.6 Diagnosis of a child with symptoms of wheezing [33].

Is this related to an allergic reaction?

10 kU_A/l* corresponds to **30%** probability of allergy relation

100 kU_A/l* corresponds to **60%** probability of allergy relation

Will the present wheeze develop into persistent wheeze during next years to come?

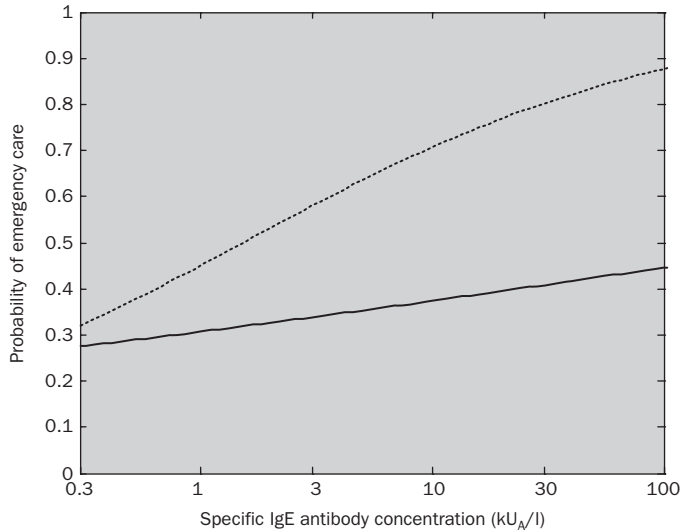
10 kU_A/l* corresponds to **50%** probability of development into persistent wheeze

30 kU_A/l* corresponds to **90%** probability of development into persistent wheeze

* sum of sIgE values for mite, cat and dog

Since asthma exacerbations are well known with viral infections, much focus has been placed on the role of viral infections and the susceptibility of asthmatic subjects to such infections. Recent information points to extensive synergistic effects of virus infections and allergic inflammation both in children and adults [9,44–45]. Furthermore, in a recent study it was reported that not only was being sensitized a risk factor but that the risk increased with increasing specific IgE levels [44]. Further similar analysis of results in schoolchildren showed that the sum of mite, cat and dog specific IgE was associated with an increased risk of hospital admission with an asthma exacerbation. Thus, a sum of 10 kU_A/l sIgE increased the risk almost 2.5 times and a sum of 30 kU_A/l increased the risk three-fold. This

Fig. 1.3 The probability that a patient with asthma will need emergency care in relation to only sIgE antibodies and exposure to allergens (solid line) and virus infection together with sIgE antibodies and exposure to allergens (dotted line). With permission from the General Practice Airways Group [7,44].



corresponds to a 30–40% probability of being admitted to hospital due to an asthma exacerbation (Fig. 1.3, solid line) [7,44]. Elevated sIgE levels and exposure to allergens in conjunction with a virus infection appear to strongly increase the probability of hospitalization among childhood asthmatics over and above that of the sIgE alone. In such cases, a sum of as little as 3 kU_A/l of sIgE may correspond to a 60% probability, and a sum of 30 kU_A/l as greater than a 80% probability, of hospital admission (Fig. 1.3, dotted line) [7,44]. This information points to the importance of optimized allergy management of patients at risk and measures undertaken to both decrease allergen exposure in relation to the sIgE levels and include prescription of increased anti-inflammatory therapies particularly during periods of time when other contributing factors like virus infections are likely.

To use quantitative IgE information in a clinical setting, a system for highly precise, reproducible, and accurate determination of the IgE antibody levels is essential [46]. It has to be emphasized that this approach is not generally applicable and has been well documented with one testing modality (ImmunoCAP) after very careful standardization [46]. Data from the system that has been used for developing quantitative probability models attributing the risk of clinical disease cannot be generalized. Since the IgE results obtained using other test systems may differ significantly [22,23], prescribing clinicians and testing laboratories need to be aware of possible differences in the results from different systems [24]. Similar results may be obtained using carefully performed skin prick tests with high quality extracts and precise assessment of the weal size. However, this is unlikely to be applicable to a general clinical setting, where skin tests are performed on a routine basis by different operators using a range of different allergen extracts which may not be standardized [33,47].

The natural course of allergy development (Allergy March)

In many or most allergic children, their symptoms evolve along a particular path (Allergy March). Symptoms of eczema and wheeze as well as sensitization and IgE antibody formation to first food and later inhalant allergens may occur early during this path. These symptoms can evolve from mild eczema and wheeze into severe conditions. However, on the contrary about half of the children lose their symptoms when growing older. Although early wheeze is frequently triggered by virus infection, it may also have an allergic component. It has been noted that two out of five children are sensitized and have sIgE antibodies to inhalants but only 25–30% of those develop asthma [14,15,48]. Of asthmatics in general about two out of three asthmatics are sensitized and have sIgE antibodies to inhalant allergens. Furthermore, those having higher sIgE antibody levels have a higher likelihood of allergic wheeze and asthma developing over time [14,15,48].

A major concern for many patients is to know whether their disease will persist or resolve. In a young child with wheeze there are several options available for improving the accuracy of the diagnosis—the clinical history with information on family history, family smoking habits and other environmental exposures, all adding a certain level of risk of the diagnosis (see Box 4). Some results have shown that the persistence of wheeze at age 5 years can be predicted using the sIgE antibody levels at age 3 years [33]. For example, 10 kU_A/l of sIgE in the presence of a positive family history gives a probability of current wheeze of about 90%, corresponding to a 30-fold risk. The same 10 kU_A/l of sIgE, even with a negative family history, gives a probability of current wheeze of 65%, corresponding to an eight-fold increased risk (Fig. 1.2). When evaluating sIgE to allergens in this context, sIgE to food must not be neglected even if the symptom is asthma [49–50]. Together with the patient's case history, such information would allow the physician to reveal the likelihood of allergy and exposure to a specific allergen as being the driver of symptoms and disease. Furthermore, this would allow the physician to adopt the appropriate therapy accordingly, since it is not likely that a patient with very low sIgE level to relevant allergens would benefit from allergen-specific treatment and corticosteroids.

In situations when the allergy is expected to disappear or is already fading away, sIgE antibody determinations may also be useful [51]. Declining levels of sIgE antibodies can be taken as a marker of decreased allergen exposure, or of emerging allergen tolerance. This has been well documented in children with food allergy, where a high (>30 kU_A/l) level of sIgE is seen to slowly decrease (over more than 12 months) which indicates that tolerance may not be evolving, whereas a moderate to low value (approx 10 kU_A/l), decreasing by more than 75% in 12 months, is highly predictive of evolving tolerance [51]. Again such information is not revealed by tIgE.

Conclusion

In allergy, clinicians frequently follow a ‘trial and error’ process, by progressing directly from patients presenting signs and symptoms to pharmacotherapy. Empirical management may result in inadequately controlled symptoms and repeat office visits, as well as unnecessary referrals and drug use. The addition of sIgE antibody results improves the accuracy of diagnosis. The goal by using a sIgE antibody test is to change the probability that a patient has a certain diagnosis from the one without using such a test. Thus, allergy testing should be considered as an adjunct to the clinical history and physical examination similar to other diseases such as hypercholesterolaemia and diabetes. In these situations all information from case history, physical examination and diagnostic test results is evaluated together to guide optimal therapeutic decision-making. However, in some patients despite an intermediate or high probability of allergy, as assessed by history and physical examination, the sIgE antibody results may prove to be negative. In such cases, extensive analysis of the case history and empirical drug therapy is warranted with further testing for those who do not respond adequately [16,17,52].

It must also be pointed out that allergic diseases are variable and can change over time from a sensitized situation without any obvious symptoms, to symptoms that may change from eczema to wheeze to rhinitis, the so-called Allergy March, and sometimes even escape to a symptom-free state.

Generally, all individuals with severe and/or persistent/or recurrent symptoms like those typically ensuing from allergic reactions should be examined for an allergic condition and tested for which allergens may be the cause of those symptoms [53]. Furthermore, the age of the individual, the family history as well as the character of the symptoms, including whether they are diurnal and/or occur during certain periods of the year [53], need to be evaluated during the diagnostic process and should be taken into account when evaluating the specific IgE antibody levels.

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