

Diagnosis of Pediatric Allergy

From History to Clinical-Functional Examination

The diagnosis of atopic disease has particular characteristics, since pediatric allergy is significantly different from adult allergy. It is essentially based on a detailed family and personal history. The purpose of the history is not only to confirm or exclude a clinical pattern of suspected allergic disease, but also to identify and demonstrate the pertinent etiological factors. Diagnostic tests can help the physician if they are considered in connection to symptoms, but not if evaluated individually: infants and boys are too often labeled as atopic only because skin prick tests (SPTs) or RAST (radio-allergosorbent tests) are positive. We cannot continue without underlining the special prudence that must be reserved for the possible inappropriateness of parent declarations, mainly when symptoms are not reported in a simple and objective way. However, to facilitate information exchange, it is necessary to take advantage of what parents report, listen to them, encouraging them to talk: a keen and accurate patiently gathered history concretely helps the pediatrician to individuate the direct causal relationship. Adler et al [2] have shown that if on the one hand SPTs, RAST and MAST-CLA tests were positive in 6.7% of asthmatic children but their parents declared they were affected with food allergy (FA), on the other at least one test was positive in 23.3% of children declared healthy [2]. In several cases we shall find a notable discrepancy between data referred to by families and data ascertained during the medical visit (Table 6.1).

Although in the last few decades the very great and multiform technological progress has in various ways changed the approach to children with atopic disease, diagnosis is very important, since both prophylaxis and the early institution of specific treatments are able to positively modify the natural history of atopic disease (Fig. 6.1) [179]. Therefore, diagnosis covers several points:

1. History
2. Medical examination
3. Diagnostic testing (in vivo and in vitro)
4. Specific provocation tests
5. Pulmonary function testing (PFT)

Table 6.1. Factors provoking asthma according to parents

Factors	%
Infections	70
Weather changes	49
Passive smoke	22
Physical exercise	17
Strong odors	7
Emotions	4
Food allergy	2

Data from personal results of a polycentric epidemiological study in Italian allergic children (unpublished data).

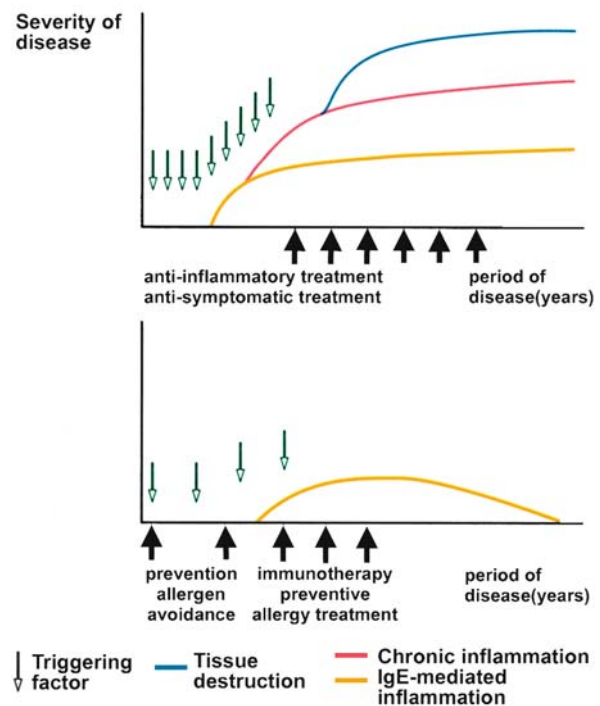


Fig. 6.1. The value of early diagnosis. The specific diagnosis of IgE-mediated allergic disease is very important in the early phase of the disease. By environmental prophylaxis and early treatment, it is conceivable to modify the natural history of allergy. Nevertheless, when the disease is already well-established, an antisymptomatic and/or anti-inflammatory treatment will become necessary. (Modified from [179])

The diagnosis of atopic disease in children, and above all the identification of pathogenic factors, needs the cooperation of a specialist center.

Allergy History

An accurate history is of paramount importance, because it is the key to gathering relevant information. After collecting a complete and accurate record, the nature, characteristics, frequency, as well as the possible severity of allergic symptoms will be defined [175]. As the interview continues, it is possible to exclude different conditions that present similar patterns. Subsequently, the clinical manifestations are explored: from the combined examination, specifically medical and with the possible help of diagnostic testing, the diagnosis is established [127]. To facilitate information exchange, listen patiently to the parent describing the history of the present illness as he (or she) deems appropriate, making the parent(s), who are generally unprepared and anxious, comfortable. If the baby weeps or screams or is naughty, the doctor may suggest entrusting the child to a parent until the moment of the visit, also to assure a greater concentration for both physician and parent(s).

Experience shows that:

1. History, although accurate, can be silent, thus complicating the diagnosis.
2. To ensure that the history is careful and detailed, the doctor should be friendly and unhurried, repeating if necessary the same question, even if only in a different form.
3. Nothing should be neglected, yet all data should be well investigated and properly arranged.
4. It is better to ask more questions or note more data, rather than to overlook them in the belief that the issues have been focused.
5. To continue methodically it is convenient to have a mental checklist at hand.
6. A record-chart or a computerized program with pre-arranged questions will make the task easier, but no issue should be neglected: with time, the opportunity of adding new questions or better detailing the already present ones can be evaluated.

The utility of well-organized and drafted record-charts is also underlined by the likelihood (or necessity) of updating them, considering second thoughts and unceasingly updating the written records with further data, which may often be recalled or provided in subsequent visits. Therefore, depending on his/her mood, the interviewer should decide whether or not to return to the history at a later time. A meaningful history therefore represents a diagnostic moment of great significance, even if it can be stressful, because history taking requires patience, listening and synthesis and abstraction abilities, as well as a great availability.

Family Allergy History

When the family history is positive, the chance that the patient is predisposed or sensitized and that some or all of his/her symptoms have an atopic origin increases: in this case it is helpful to recall the risk rates indicated in Tables 4.9–4.11. The immediate history of each family member is of the utmost relevance and should include both the mother and father of the child, as well as any information regarding other relatives, based on the family atopy score (FAS), as shown in Table 3.9. Moreover, because of the growing exposure to different cultures, medico-therapeutical trends not necessarily a part of our training, and our increasingly frequent encounters with citizens of other countries or continents, it is timely to investigate probable adhesions to homeopathic therapy and/or clinical ecology, as well as the family's cultural or religious eating habits.

Starting an immunological diagnosis, several questions must be answered, including unexplained miscarriages, cases of early death, morbilliform rashes during the neonatal period, early candidiasis or subsequent severe and recurrent infections, etc., leading to a PID (primary immunodeficiency), or whether addict parents have a child with ID, or as yet unexplained causes, as shown by infections from opportunistic germs, etc., suggesting a possible HIV infection.

Personal Allergy History

Following the protocol established by our division, we first investigate the mother's previous pregnancies, the related pregnancy and delivery, the neonatal period, alimentation, growth and subsequent development. If the mother smokes, ask whether she continued during or after the pregnancy and how many cigarettes she smoked or smokes daily. Regarding the type of delivery and the neonatal period, inquire whether there was any complication and/or the newborn was hospitalized for any disorder. Then accurately examine the type of feeding during the very first days, including the administration of colostrum and/or formulas different from breast milk in the maternity ward as supplements (Chap. 3). Also determine the month of birth, because there are potential implications for respiratory allergy (Figs. 4.10, 4.11). Table 5.5 shows, according to the child's age, which atopic disease will most probably affect him (her).

Inquire into the type of feeding (based on the record-chart or mental checklist) with more or less detailed questions (depending on the child's age). When feeding difficulties play a crucial role, it is timely to determine the onset of the problem with all the essential episodes, evaluating the child's growth in terms of weight and height.

Past and Present Allergy History

The past allergy history can give information directly related to the presenting symptoms such as episodes of anaphylactic shock, dermatitis, urticaria, vomiting, rhinitis, otitis, conjunctivitis, bronchitis, food allergy (FA), apparent multiple sensitizations, etc. In young children, episodes of vomiting and/or diarrhea, colic, and itching can be significant complaints. Itching is a common finding in AD (atopic dermatitis) and could be the first sign of an underlying disease. The purpose is now to define allergic symptoms, their onset, seat, intensity, duration, remissions or recurrence, etc. There may be a potential association with related allergy problems, viral or bacterial infections of the respiratory or gastrointestinal tracts. It is essential to collect information on temporal relationships and precipitating events, frequency of bettering or worsening, possible complications and/or relapses, treatments given and their responses. Then go on with the present allergy history to gather data on the age of onset and chronological sequence of symptoms: perennial or seasonal, or a daily, weekly, monthly, yearly occurrence. At this level, the decision is directed to what is most appropriate: selecting a diversified allergy history based on the prominent symptom's group, either AD-FA or asthma rhinoconjunctivitis.

Present Allergy History for Atopic Dermatitis and Food Allergy

When FA is suspected, the related history should be centered above all on the alimentation in the very first days of life and the type of feeding: exclusively maternal or supplemented and for how long, the diet prescribed to the nursing mother or, in case of bottle feeding, whether cow's milk (CM) or special formulas were used (Tables 6.2, 6.3) [32, 175].

Questions now explore at what age solid foods were introduced and which ones, verifying if necessary the data in Table 4.30, the age of onset and nature of symptoms, whether general symptoms were or are present such as shock, urticaria, skin rashes, wheezing, swellings, anemia, etc., and intestinal symptoms such as vomiting, diarrhea, colic, intercurrent infections, etc.

Starting with skin manifestations, note their morphology, time of onset, localization and timing of the lesions, also in view of the possible differential diagnosis with the seborrheic dermatitis or other skin affections. Note the relatively common contact urticaria associated with food antigens (Chap. 8).

Begin with a detailed description of symptoms, including the food suspected of provoking reactions, the time elapsed between food ingestion and symptom onset, the type of suspected food, whether it was fresh, raw, or cooked, conserved or lyophilized, the quantity of food that was necessary to produce the development of

Table 6.2. History pitfalls to be evaluated with attention when food allergy is suspected

Family history
Growth and development progression
Parents giving misleading indications
Dietetic, cultural or religious practices (vegetarians, Hebrews, Muslims, etc.)
Suspected food
Freshness and/or cooking method
Ingested amount
Interval between ingestion and reaction
Digestion and absorption
Possible contaminations
Possible cumulative effects
Relapses after ingestion of the same food
Probable dietetic or therapeutic measures

Data from [32].

Table 6.3. Frequent causes of confusion due to parents' misleading interpretations

Inclination to attribute all the clinical manifestations of the child to the last ingested food and to describe clinical findings similarly to one's own food allergy or that of a family member
Belief that a previously eliminated food is the responsible one, even if its exclusion was not productive
Probable confusion between aversion for a food and a true allergy
Tendency to interpret as an allergy the simple aversion for a food
Propensity to introduce arbitrary modifications to the diet or treatment
Propensity to set up inappropriate diets with consequent nutritive deficits

Data from [175].

symptoms and their extent, whether similar symptoms occurred on other occasions when the food was consumed and the relative management, the response to diets and/or treatment, the chronology of occasional relapses or multiple sensitizations and the symptom outcome [34]. A "virgin" case is not always seen: diets of varying types have often been arranged, recommended by several specialists, or prepared directly at home even before consultation (Chap. 9).

Regarding medications, include vitamin and mineral supplements.

When the history indicates immediate symptoms, a cause-effect relation is easily suspected. Diagnosis will be more demanding in the following cases:

1. Late reactions (even up to 15 days).

2. Interferences of additional foods.
3. Multiple sensitizations.
4. A presumed sensitization is related to breast milk priming, for example AD in exclusively breast-fed children.
5. Severe manifestations (anaphylaxis) occurring at the first introduction of a food, apparently without a previous direct sensitization (supplements in the neonatal nursery), especially when the history is silent.

When a clear correlation cannot be established, particular attention should be focused on possible temporal or environmental relationships, including infant's age, the year, season, residence at home or in other people's home, households, relatives, baby sitters, etc.

Two different occurrences can be delineated in this approach: FA in its strict sense, characterized by hypersensitivity of the IgE-mediated type, documented by specific positive tests, or food intolerance, not sustained by IgE-mediated mechanisms (Chaps. 9 and 10).

Present Allergy History for Urticaria and Angioedema and Additional Skin Allergies

Clarify whether urticaria and angioedema are isolated or associated, or whether there are hereditary forms (hereditary angioedema) or acquired forms (apparently primary, associated with other affections, or physical forms). Although it is important to consider the main pathogenic causes, it is also critical to select them based on a single clinical history, especially when urticaria is induced by medications, food and/or contact. However, if a physical form is prevalent, Chap. 8 should be consulted for the diagnosis, as for the allergic contact dermatitis (ACD) allergic vasculitis, and urticaria caused by additives.

Present Allergy History for Asthma Rhinoconjunctivitis

The key question is whether symptoms mostly of a respiratory type refer to past episodes of wheezing, bronchiolitis, relapsing cough or bronchitis, recurrent respiratory infections, pertussis, bronchopneumonia, with special emphasis on the time or seasonal vs perennial appearance, course, intensity and therapeutic interventions. In older babies, also investigate a possible exposure of the upper airway: rhinitis (rhinorrhea, cough, sneezing, etc.), otitis (serous, recurrent, chronic), maxillary sinusitis, feasible intervention of (adeno)tonsillectomy, and the related causes and outcome. The chance that pneumonia and/or pertussis and/or persisting cough may underlie an unidentified asthma case should not be neglected, also because the trend of interchangeably employing the terms of asthma and bronchitis in children aged <5 years seems to be widespread:

several young asthmatics were admitted to hospital with diagnosis of pneumonia or bronchitis [144].

If the child has suffered from asthmatic attacks, additional specific questions aim at determining what age the first episode took place, if respiratory symptoms are seasonal or perennial, then the yearly number of episodes, their severity and duration (dyspnea, shortness of breath), onset modalities, chronological sequence of breakthroughs, visits to emergency wards, hospitalizations, time course of symptoms and selective triggering factors (Table 5.11). Inquiry about seasons, climate, barometer and/or altimeter variations, places, indoors or outdoors, food, day or night, exercise-induced asthma (EIA), pets, pollens, passive smoke, odors, emotions, drugs, etc. is necessary. One may then be able to ask questions of the child beginning at ≈7 years of age such as night/day worsening, upon waking, during cleaning, in meadows or in the country, improvements, outdoors or in dry areas, yearly periods highlighted by more evident or attenuated symptoms.

As far as medication is concerned, the following must be recorded: intermittent or continuing treatment, routes of administration, daily or alternate-day dosage, whether or not asthma has provoked a reduction of physical activity, sleep, and school attendance, participation in social events, limitation in the use of public means of transportation and the capacity of going up or down stairs, etc. [29].

When rhinoconjunctivitis is suspected, one should check whether or not there are watery or purulent rhinorrhea, sneezing even upon waking, nasal obstruction and itching, oral respiration, postnasal drip, and mucus; eye findings such as tearing, itching and/or burning, eye redness, photophobia, edema, secretions; or allergic symptoms often associated with and related to otitis, including itching, otalgia, frequent infections, or general manifestations such as migraine, fatigue and possible secondary complications, including chronic nasal obstruction (CNO), sinusitis, disturbances of both smell and hearing, or sleeping, nasal hemorrhage, superinfections, etc. Similarly, we suggest thoroughly investigating whether parents report recurrent colds and bronchitis, chronic rhinitis and the like. All possible differential diagnoses should likewise be taken into account.

Environmental History

The allergy history should be completed by collecting information on the child's environment and living habits.

This includes the subject's home, the parents' or relatives' homes, as well as a possible vacation home:

- Location: urban, rural, in the mountains, at the sea. If urban, evaluate the degree of environmental pollution (severe, moderate, slight).
- Plants: type and location (indoor, outdoor); trees, weeds, grasses in the vicinity.

- Dampness, localized or generalized, air conditioning, humidifiers or fans, type of heating, air-heating, type of filters and frequency of cleaning and changes, fuel oil/gas/coal/wood heating, existence of fireplace, stoves, etc.

Bedrooms

- Location: basement or which floor
- Mattresses and pillows, type of filling (wool/down/hair/foam rubber or box-springs), encasing and purchase date
- Carpets and rugs, wall-to-wall carpeting, bedside rugs; wallpaper, curtains: if present, which material (cotton, nylon, etc.), whether washable and frequency of washing
- Furniture (upholstered furniture, etc.). If there is a closet containing household linen/clothes in the room where the child sleeps or studies, ask whether closet doors are open or closed, or rarely opened (at the change of season, etc.);

Child's Bedroom

- Other occupants, bed characteristics: when the beds have the same characteristics, return to the previous point
- Stuffed, plush toys, and whether kept in bed
- Pets (past, present and future, how long in household), which species, and whether kept in bed
- Indoor smoking: parents, relatives, regular visitors, locations allowed
- Stress: inquire whether or not there are causes for it
- Day-care facilities, baby-sitters: inquire about the location and environmental characteristics of daycare facility or child's schools, whether child consumes meals, snacks, etc., prepared locally there

Taking into consideration the pros and cons of the history, we suggest that the pros such as maximal convenience, absolutely low cost, direct contact with the child and his/her parents, and 100% noninvasiveness are immediately appreciated. If accurately done it may reduce the costs of further testing; the contras are represented by an evident subjectivity, the time required and the necessity of ensuring the child's (and parents') compliance [179].

Medical Examination

Some characteristic aspects can suggest the diagnosis such as allergic salute, infraorbital edema, nasal congestion, cough, Hertoghe's sign, etc.

In a child with suspected dermatitis with FA and skin manifestations, we observe the nutritional state, the type, localization and extension of lesions, usually corresponding to the child's age and the lesion severity.

Body diagrams can be used (Figs. 6.2, 6.3), which arbitrarily divide the body surface into 20 areas. For each area the eczema is assessed in terms of:

- Redness (R)
- Vesicles, oozing/crusting (V)
- Excoriations (E)
- Lichenification (L)

Each type of lesion is given a score on a scale of 0 (none) to 3 (severe). The use of a scoring system quantifies possible improvement (or worsening) of skin lesions at subsequent visits. Note the data on the diagram to compare this with the next one.

Another method is based on different scores [20]:

0: Healthy child, no lesions

1: Mild, with scarce erythematous areas, with or without occasional scratching

2: Moderate, with areas of erythema, macule and scaly lesions, with or without obvious scratching, lasting >2 min each time

3: Severe, with marked and diffused erythema (>50%), scaly lesions also diffused (>25%), vesicles and/or pilary erection and incessant and conscientious scratching

The European Task Force on Atopic Dermatitis [161] has devised a composite index, applied in our division, the SCORAD (scoring of AD), which also takes into account lesion severity and subjective symptoms (Figs. 6.4–6.18) [161]. It is divided into three scores:

A Extent, according to the indications shown in Fig. 6.19 [161], which proposes a different evaluation of lesions for children <2

B Intensity, regarding the different symptoms, equally scored 0–3

C Pruritus and sleep loss (mean of the last 3 days or nights), each graded 0–10

Once A, B and C are calculated, the formula $(A:5) + (B \times 3.5) + C$ is applied; the highest score in an infant <2 is $(103:5) + (18 \times 3.5) + 20$, thus $A 20 + B 63 + C 20 = 103$. In children aged >2, the calculation is equal because the total of A is 102. This way great emphasis is given to the symptom intensity: A (extent) and C (symptoms) are each equal to 19.4% and extent to 61.2%. Definitions of commonly used skin descriptive terms are summarized in Table 6.4.

In all children, the medical examination should include the auscultation of the chest, the examination of the abdomen and, depending on the circumstances, of ears, nose, and eyes. Also necessary is the accurate determination of heart (HR) and respiratory rates (RR), as well as the anthropometric evaluation with percentiles (Appendices 6.1–6.4), also considering growth and nutritional state. In asthmatic children, the medical examination should include spirometry and the peak expiratory flow rate (PEF or PEFR) (see “Additional Tests”).

Table 6.5 [175] outlines the clinical symptoms that can be helpful in differential diagnosis [175] and Table 6.6 [104] concludes with risk factors for wheezing <3 and childhood asthma in children <3 years [104].

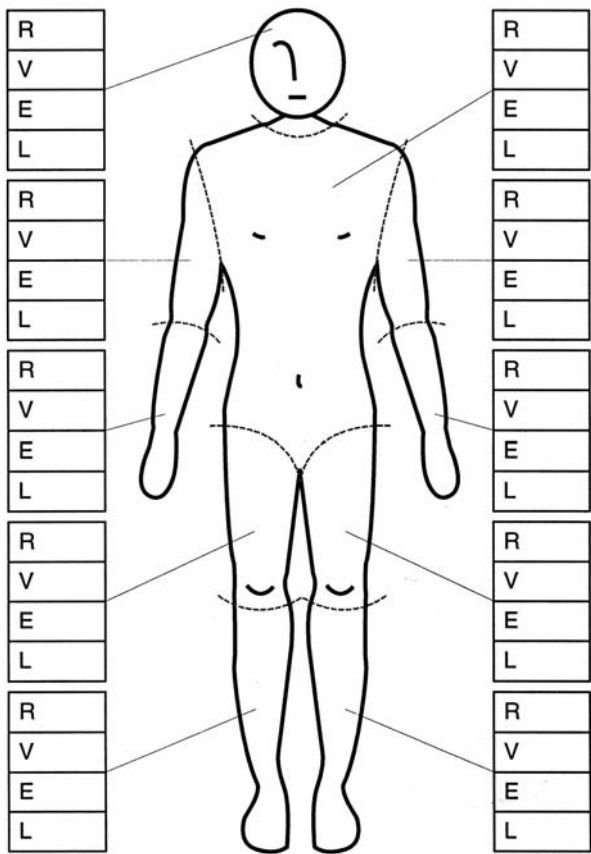


Fig. 6.2. Body diagram from our division for the evaluation of skin lesions: front view

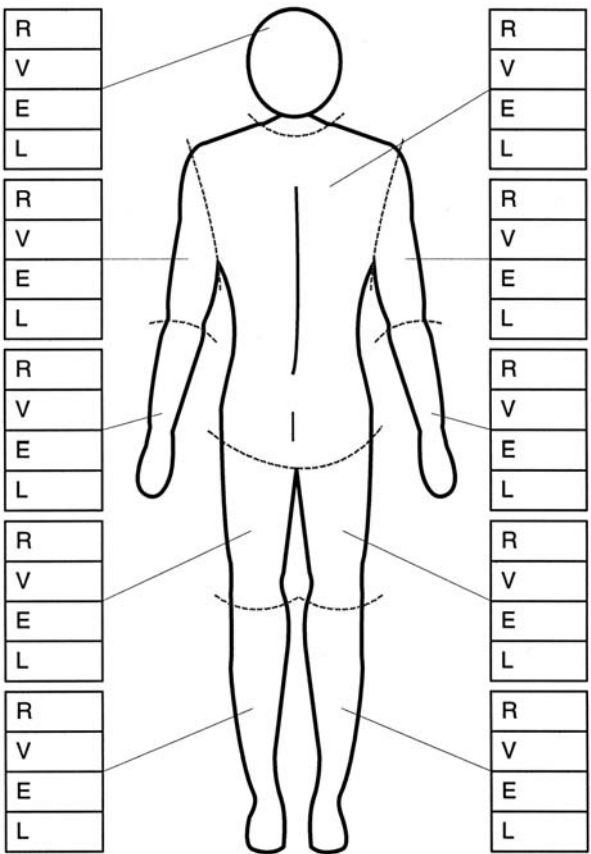


Fig. 6.3. Body diagram from our division for the evaluation of skin lesions: rear view

Photographic Atlas to Illustrate the Scoring System



Fig. 6.4. Erythema, grade 1



Fig. 6.5. Erythema, grade 2

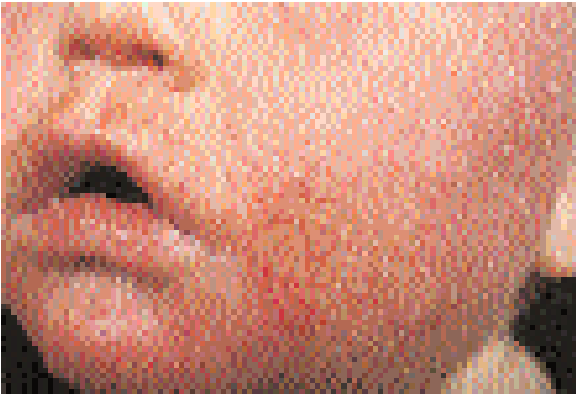


Fig. 6.6. Erythema, grade 3



Fig. 6.7. Edema, papulation, grade 1

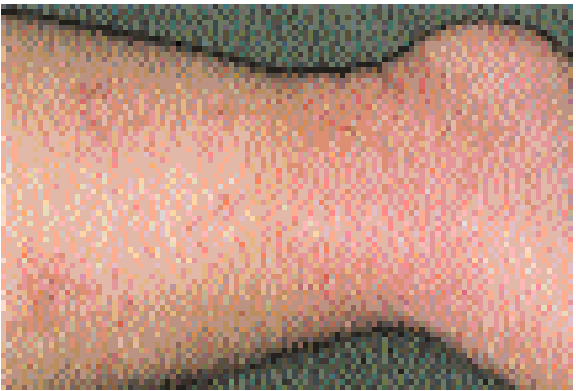


Fig. 6.8. Edema, papulation, grade 2



Fig. 6.9. Edema, papulation, grade 3



Fig. 6.10. Oozing, crusts, grade 1



Fig. 6.11. Oozing, crusts, grade 2



Fig. 6.12. Oozing, crusts, grade 3



Fig. 6.15. Excoriations, grade 3



Fig. 6.16. Lichenification, grade 1



Fig. 6.13. Excoriations, grade 1



Fig. 6.17. Lichenification, grade 2



Fig. 6.14. Excoriations, grade 2



Fig. 6.18. Lichenification, grade 3

SCORAD PSORIASIS LESION INDEX ON ATOPIC DERMATITIS																	
Child Name: _____		Date: _____															
Date of Birth: _____		Sex: _____															
Place of Visit: _____		Country: _____															
DEFINITION PHYSICIAN: _____																	
Topical Steroid use: Did you apply steroid to _____ (square of body) / month Number of times / month: _____																	
Figures: In pen and black, for children under two years																	
A: COUNT Place index on area involved: _____																	
B: INTENSITY _____		C: SUBJECTIVE SYMPTOMS PRURITUS-ITCHING: _____															
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="padding: 2px;">No. lesions</th> <th style="padding: 2px;">intensity</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">Erythema</td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">Elevated Papules</td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">Crusts/scales</td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">Excoriations</td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">Lichenification</td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">Folliculitis</td> <td style="padding: 2px;"></td> </tr> </tbody> </table>	No. lesions	intensity	Erythema		Elevated Papules		Crusts/scales		Excoriations		Lichenification		Folliculitis		<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="padding: 2px;">PLANS OF CALCULATION</th> </tr> </thead> <tbody> <tr> 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PLANS OF CALCULATION																	
(A) x (B) x (C) x (D) x (E) x (F) x (G) x (H) x (I) x (J) x (K) x (L) x (M) x (N) x (O) x (P) x (Q) x (R) x (S) x (T) x (U) x (V) x (W) x (X) x (Y) x (Z) x (AA) x (AB) x (AC) x (AD) x (AE) x (AF) x (AG) x (AH) x (AI) x (AJ) x (AK) x (AL) x (AM) x (AN) x (AO) x (AP) x (AQ) x (AR) x (AS) x (AT) x (AU) x (AV) x (AW) x (AX) x (AY) x (AZ) x (BA) x (BB) x (BC) x (BD) x (BE) x (BF) x (BG) x (BH) x (BI) x (BJ) x (BK) x (BL) x (BM) x (BN) x (BO) x (BP) x (BQ) x (BR) x (BS) x (BT) x (BU) x (BV) x (BW) x (BX) x (BY) x (BZ) x (CA) x (CB) x (CC) x (CD) x (CE) x (CF) x (CG) x (CH) x (CI) x (CJ) x (CK) x (CL) x (CM) x (CN) x (CO) x (CP) x (CQ) x (CR) x (CS) x (CT) x (CU) x (CV) x (CW) x (CX) x (CY) x (CZ) x (DA) x (DB) x (DC) x (DD) x (DE) x (DF) x (DG) x (DH) x (DI) x (DJ) x (DK) x (DL) x (DM) x (DN) x (DO) x (DP) x (DQ) x (DR) x (DS) x (DT) x (DU) x (DV) x (DW) x (DX) x (DY) x (DZ) x (EA) x (EB) x (EC) x (ED) x (EE) x (EF) x (EG) x (EH) x (EI) x (EJ) x (EK) x (EL) x (EM) x (EN) x (EO) x (EP) x (EQ) x (ER) x (ES) x (ET) x (EU) x (EV) x (EW) x (EX) x (EY) x (EZ) x (FA) x (FB) x (FC) x (FD) x (FE) x (FF) x (FG) x (FH) x (FI) x (FJ) x (FK) x (FL) x (FM) x (FN) x (FO) x (FP) x (FQ) x (FR) x (FS) x (FT) x (FU) x (FV) x (FW) x (FX) x (FY) x (FZ) x (GA) x (GB) x (GC) x (GD) x (GE) x (GF) x (GG) x (GH) x (GI) x (GJ) x (GK) x (GL) x (GM) x (GN) x (GO) x (GP) x (GQ) x (GR) x (GS) x (GT) x (GU) x (GV) x (GW) x (GX) x (GY) x (GZ) x (HA) x (HB) x (HC) x (HD) x (HE) x (HF) x (HG) x (HH) x (HI) x (HJ) x (HK) x (HL) x (HM) x (HN) x (HO) x (HP) x (HQ) x (HR) x (HS) x (HT) x (HU) x (HV) x (HW) x (HX) x (HY) x (HZ) x (IA) x (IB) x (IC) x (ID) x (IE) x (IF) x (IG) x (IH) x (II) x (IJ) x (IK) x (IL) x (IM) x (IN) x (IO) x (IP) x (IQ) x (IR) x (IS) x (IT) x (IU) x (IV) x (IW) x (IX) x (IY) x (IZ) x (JA) x (JB) x (JC) x (JD) x (JE) x (JF) x (JG) x (JH) x (JI) x (JJ) x (JK) x (JL) x (JM) x (JN) x (JO) x (JP) x (JQ) x (JR) x (JS) x (JT) x (JU) x (JV) x (JW) x (JX) x (JY) x (JZ) x (KA) x (KB) x (KC) x (KD) x (KE) x (KF) x (KG) x (KH) x (KI) x (KJ) x (KK) x (KL) x (KM) x (KN) x (KO) x (KP) x (KQ) x (KR) x (KS) x (KT) x (KU) x (KV) x (KW) x (KX) x (KY) x (KZ) x (LA) x (LB) x (LC) x (LD) x (LE) x (LF) x (LG) x (LH) x (LI) x (LJ) x (LK) x (LL) x (LM) x (LN) x (LO) x (LP) x (LQ) x (LR) x (LS) x (LT) x (LU) x (LV) x (LW) x (LX) x (LY) x (LZ) x (MA) x (MB) x (MC) x (MD) x (ME) x (MF) x (MG) x (MH) x (MI) x (MJ) x (MK) x (ML) x (MM) x (MN) x (MO) x (MP) x (MQ) x (MR) x (MS) x (MT) x (MU) x (MV) x (MW) x (MX) x (MY) x (MZ) x (NA) x (NB) x (NC) x (ND) x (NE) x (NF) x (NG) x (NH) x (NI) x (NJ) x (NK) x (NL) x (NM) x (NN) x (NO) x (NP) x (NQ) x (NR) x (NS) x (NT) x (NU) x (NV) x (NW) x (NX) x (NY) x (NZ) x (OA) x (OB) x (OC) x (OD) x (OE) x (OF) x (OG) x (OH) x (OI) x (OJ) x (OK) x (OL) x (OM) x (ON) x (OO) x (OP) x (OQ) x (OR) x (OS) x (OT) x (OU) x (OV) x (OW) x (OX) x (OY) x (OZ) x (PA) x (PB) x (PC) x (PD) x (PE) x (PF) x (PG) x (PH) x (PI) x (PJ) x (PK) x (PL) x (PM) x (PN) x (PO) x (PP) x (PQ) x (PR) x (PS) x (PT) x (PU) x (PV) x (PW) x (PX) x (PY) x (PZ) x (QA) x (QB) x (QC) x (QD) x (QE) x (QF) x (QG) x (QH) x (QI) x (QJ) x (QK) x (QL) x (QM) x (QN) x (QO) x (QP) x (QQ) x (QR) x (QS) x (QT) x (QU) x (QV) x (QW) x (QX) x (QY) x (QZ) x (RA) x (RB) x (RC) x (RD) x (RE) x (RF) x (RG) x (RH) x (RI) x (RJ) x (RK) x (RL) x (RM) x (RN) x (RO) x (RP) x (RQ) x (RR) x (RS) x (RT) x (RU) x (RV) x (RW) x (RX) x (RY) x (RZ) x (SA) x (SB) x (SC) x (SD) x (SE) x (SF) x (SG) x (SH) x (SI) x (SJ) x (SK) x (SL) x (SM) x (SN) x (SO) x (SP) x (SQ) x (SR) x (SS) x (ST) x (SU) x (SV) x (SW) x (SX) x (SY) x (SZ) x (TA) x (TB) x (TC) x (TD) x (TE) x (TF) x (TG) x (TH) x (TI) x (TJ) x (TK) x (TL) x (TM) x (TN) x (TO) x (TP) x (TQ) x (TR) x (TS) x (TT) x (TU) x (TV) x (TW) x (TX) x (TY) x (TZ) x (UA) x (UB) x (UC) x (UD) x (UE) x (UF) x (UG) x (UH) x (UI) x (UJ) x (UK) x (UL) x (UM) x (UN) x (UO) x (UP) x (UQ) x (UR) x (US) x (UT) x (UU) x (UV) x (UW) x (UX) x (UY) x (UZ) x (VA) x (VB) x (VC) x (VD) x (VE) x (VF) x (VG) x (VH) x (VI) x (VJ) x (VK) x (VL) x (VM) x (VN) x (VO) x (VP) x (VQ) x (VR) x (VS) x (VT) x (VU) x (VV) x (VW) x (VX) x (VY) x (VZ) x (WA) x (WB) x (WC) x (WD) x (WE) x (WF) x (WG) x (WH) x (WI) x (WJ) x (WK) x (WL) x (WM) x (WN) x (WO) x (WP) x (WQ) x (WR) x (WS) x (WT) x (WU) x (WV) x (WW) x (WX) x (WY) x (WZ) x (XA) x (XB) x (XC) x (XD) x (XE) x (XF) x (XG) x (XH) x (XI) x (XJ) x (XK) x (XL) x (XM) x (XN) x (XO) x (XP) x (XQ) x (XR) x (XS) x (XT) x (XU) x (XV) x (XW) x (XX) x (XY) x (XZ) x (YA) x (YB) x (YC) x (YD) x (YE) x (YF) x (YG) x (YH) x (YI) x (YJ) x (YK) x (YL) x (YM) x (YN) x (YO) x (YP) x (YQ) x (YR) x (YS) x (YT) x (YU) x (YV) x (YW) x (YX) x (YY) x (YZ) x (ZA) x (ZB) x (ZC) x (ZD) x (ZE) x (ZF) x (ZG) x (ZH) x (ZI) x (ZJ) x (ZK) x (ZL) x (ZM) x (ZN) x (ZO) x (ZP) x (ZQ) x (ZR) x (ZS) x (ZT) x (ZU) x (ZV) x (ZW) x (ZX) x (ZY) x (ZZ)																	

Hand writing scale:
(average for the last
3 days or nights)

PRURITUS-itching: _____
SLEEP LOSS: _____

0

10

TREATMENT:

REMARKS:

Fig. 6.19. Evaluation sheet of SCORAD severity index of AD lesions

Table 6.4. Descriptive terms useful for reporting skin lesions

Type of lesions	
Erythema: diffuse or localized redness (due to active or passive capillary hyperemia), disappearing with vitropression	
Macule: circumscribed color change, not palpable, of different form, color and dimensions, not disappearing with vitropression	
Patch: macule larger than 1 cm in diameter	
Papule: firm skin elevation (following hyperemia or phlogosis), 1 cm or less, colored or not, localized and persistent	
Wheal: evanescent elevation (due to edema), localized, consistent, pink-red or porcelaneous-white, surrounded by an erythematous flare; it is characteristic of urticaria	
Vesicle: small, clear fluid-filled elevation within the epiderm or between epiderm and derma	
Bulla: localized, clear fluid-filled elevation of varying dimensions, subepidermic or between epiderm and derma, elevated on the skin plain	
Scale: small agglomeration of horny cells, mono- or polystratified, easily detachable assuming the aspect of a thin lamella	
Characteristics of the lesions	
Number: one, some, several, many	Surface: smooth or rough
Location	Limits: net or faded
Distribution: disseminated, confluent, linear, figured	Consistency: soft, stiff
Extension: localized, regional, disseminated	Pain: to the touch
Shape: regular or irregular, roundish, annular, etc.	Aspect: mono- or polymorphous
Color: normal or abnormal pigmentation	

Table 6.5. Differential diagnosis according to clinical manifestations

Symptoms	Diagnosis to be evaluated
Airways	Asthma from inhalant allergens, foreign bodies, otitis media with effusion (OME), cystic fibrosis, IgA deficit, primary ciliary dyskinesia, dysgammaglobulinemia, anatomical defects (tracheoesophageal fistula, etc.)
Skin	Several diagnoses are possible (see Chaps. 7, 8)
Gastroenteric (diarrhea, failure to thrive, malabsorption)	
0–30 days	Food allergy, food errors, viral disease, galactosemia, disaccharidase secondary deficit, congenital lactase deficit, short bowel syndrome, intestinal lymphangiectasia, Wiskott-Aldrich syndrome
30 days–2 years	All the above-mentioned disorders, plus intestinal parasitosis, celiac disease, abetalipoproteinemia
>2 years	All the above-mentioned disorders, plus cystic fibrosis, ulcerative colitis, Crohn’s disease
(Vomiting, diarrhea, abdominal distension/pain, melena)	Surgical causes (congenital megacolon, hiatal herniae, pyloric stenosis, tracheoesophageal fistula), infections, metabolic diseases (galactosemia, phenylketonuria, disaccharidase deficit), organ-specific diseases
Blood	Sideropenic anemia: several causes are possible
Central nervous system	Headache, hyperactivity, irritability, tiredness, behavioral and sleeping troubles

Data from [175].

Diagnosis Type

Before utilizing SPTs and other diagnostic tests, it is necessary to define disease [121]. In our division we use the following operational definitions of disease:

- AD diagnosis follows the appearance of erythematous or vesicular itching skin eruptions, involving typical seats (cheeks, extensor aspects of the extremities in

infants, retroauricular sulcus), and a severity score as described in the previous section.

- For the diagnosis of urticaria defined as allergic, if appearing on at least two occasions within 1 h after exposure to a particular allergen and later to additives.
- For the diagnosis of asthma, we define the wheezing without asthma as a wheezing in the past 12 months without lifetime asthma; the wheezing with asthma as a

Table 6.6. Differentiation between wheezing and asthma in babies aged <3 years

	Wheezing <3 years	Asthma
Exogenous causes		
Allergen exposure	–	+++
Bottle-feeding	++	–
Passive smoke exposure	++	+++
Airway exposure to viral infections	++++	++
Endogenous causes		
Family history of asthma	–	++++
Atopy	+	++++
Male sex	++	+++
Immune response to infections	+++	?
Initial airway reactivity	–	++
Initial lung function	++++	?

Data from [104].

lifetime asthma with wheezing in the past 12 months; the severe wheezing as having >4 attacks of wheezing, or >1 nocturnal awakening/week due to wheezing, or speech limiting wheeze, in the past 12 months, the severe asthma as lifetime asthma with severe wheezing in the past 12 months. The wheezing is nearly always associated with upper respiratory tract infection (URTI).

- For the diagnosis of rhinitis, nasal discharge and/or blockage occurring continuously for at least 4 weeks plus the typical pale aspect of allergic mucosa on rhinoscopy, without any sign of infective rhinitis in other relatives, is required.
- For the diagnosis of gastrointestinal symptoms, recurrent colic, vomiting, and/or diarrhea after excluding ordinary eating problems, coincidental infections, and lactose intolerance.
- For the diagnosis of FA, skin, gastrointestinal, and respiratory symptoms occurring after the definite disappearance of symptoms after each of two dietary eliminations of the food in question and recurrence of identical symptoms after DBPCFC (double-blind, placebo-controlled food challenge) with the offending food, or after intake of a specific food on at least two occasions.

Results of both history and medical examination are helpful to determine which SPT is the most appropriate [127].

Immunoallergic Diagnosis

Among immunoallergic tests, in vivo tests, SPTs and provocation tests and in vitro tests are included as well as serum total and food-specific IgE (sIgE), eosinophil

count and other tests. In this chapter we do not discuss elimination diets and FCTs (food challenge tests) and tests with drugs, which are to be found in Chaps. 9 and 19. The diagnosis of autoimmune disorders, PIDs and pediatric AIDS is covered in Chaps. 18, 22 and 23, respectively.

In vivo Immunoallergic Tests

The diagnosis of allergic disease in children requires a careful and critical evaluation of laboratory test results. Serum total IgE levels and sIgE are not always correlated with history, and all different tests employed may lack specificity and/or sensitivity.

Skin Prick Tests

SPTs were devised by Blackley [18], who was allergic, by putting grass pollen on a skin scratch done on the forearm volar face, where an itching wheal surrounded by a flare developed. This method was substituted in 1912 by intradermal testing, followed by SPTs in 1924 and by prick + prick (P+P) tests in 1978. In Chap. 1 we underlined the necessity of standardization, hence the allergen concentration in the extract should be dosed in BU (biologic units) [49]. We follow the indications of the European Academy of Allergy and Clinical Immunology (EAACI) [49].

Choice of Method

The best-known method that we prefer is SPTs, although intradermal skin testing, except for specific cases (Hymenoptera, drugs), is not recommended in children, because it has an increased risk of inducing a systemic reaction and a great number of false-positive results [41]. It has been revived by the AAP (American Association of Pediatrics) as an integral part of the ritual preceding anti-measles vaccination (Chap. 9); the so-called scratch test has been largely discontinued because of its lack of precision.

Indications

SPTs consist in allergen percutaneous administration. If correctly done and with standardized extracts the advantages are: rapidity, certainty, low-cost results, ease of performance, high sensitivity and is thus reliable and reproducible [176], because it has been widely experimented. As a consequence, SPTs are the most frequently used methods for a diagnosis of IgE-mediated allergic disease where skin-sensitizing antibodies are present. When skin mast cells have surface sIgE for intruding allergens, mast cells degranulate, releasing their media-

tors, thus producing a cutaneous wheal-and-flare reaction, a type I immune reaction [49].

SPTs are more sensitive and specific in respiratory allergies, thereby representing the first-choice investigation when an IgE-mediated allergic disease elicited by aeroallergens is suspected and in asthma epidemiological studies [45]. In FA diagnosis, SPTs are less reliable, because of different factors, including the instability of some allergens, cross-reactivity between allergens belonging to different plant species or to the same species, antigenicity loss during extraction and inadequacy of allergenic extracts (see “Prick + Prick Testing”).

Age

SPTs can be done at any age, although infants can manifest less evident skin reactions than older children, since skin mast cells exhibit a lower number and express fewer IgE receptors and less mediator release, and total or sIgE values are reduced; this also applies to histamine tests. SPTs can yield reliable results even in neonates and in infants, aged even 1 [99] or 3 months [163], as we habitually practice SPTs. However, if these disturbances persist regardless of negative results, SPTs are repeated in a subsequent visit. We generally do not advise doing a large number of SPTs [37].

Seasonal Variations in SPT Reactions

No seasonal variations were disclosed other than the report of monthly influences (February and October +, July and August –) [118]. Selection of a season to perform SPTs may be important for pollen-sensitive children, who are more reactive during the pollen season since enhanced allergens by grass pollens increase wheal reactions to such allergens.

Allergens to Be Tested

In the commercial diagnostic collections, a large variety of allergens are found; nonetheless, the majority of them have no clinical significance, because either some allergens rarely cause sensitization or the child is rarely in contact with such allergens. As discussed above, we find it convenient to use mostly those allergens commonly responsible for atopic disease, taking into account the results of both history and clinical manifestations of each child. For the diagnosis of respiratory allergy, in most cases a limited group of aeroallergens are sufficient [19] (Table 1.74):

- Mites: *Dermatophagoides pteronyssinus* (Der p) (Fig. 1.80), *Dermatophagoides farinae* (Der f). It is not necessary to assess the value of *Euroglyphus maynei* (Eur m1), since it cross-reacts with Der p.

- Pet allergens such as cats (Fel d 1) and dogs (Can f 1); bird feathers, horse hairs, etc., when requested.

- Hymenoptera venoms: when suspecting a related allergy, perform the tests in hospital employing all venoms of the most widely spread insects: *Apis mellifera* (honeybee), *Vespula* spp (yellow jacket), *Polistes* spp (wasp).

- Pollens: grasses (Figs. 1.69–1.73) including *Lolium perenne* (Lol p), *Cynodon dactylon* (Cyn d), *Parietaria* (P) (Fig. 1.75–1.77), *Compositae* (Fig. 1.67, 1.74), and possibly also *Mercurialis annua* [7], *Platanus acerifolia*, *Betulaceae*, *Cupressaceae* [193], two or three trees that are more frequent in the related geographic area, in addition to emergent pollens (Chap. 12). In children positive to Lol p and Cyn d, we also test *Phleum pratense* (Phl p), *Poa pratensis* (Poa p), *Dactylis glomerata* (Dac g) and *Festuca elatior* (Fes e). When a crossed sensitization between different types of a single pollen species exists, it is often sufficient to test only one for each species. We stress that the so-called ozone hole has caused an anticipation of pollination, favoring pollen spread in geographic areas where temperature (T) is increased. Therefore, certain species, for instance P, can be detected in regions that have become climatically more favorable.

- Molds: *Alternaria alternata* (Alt a) (Fig. 1.79), *Cladosporium* (Fig. 1.78).

In the great majority of children, the likelihood of respiratory allergy can be established utilizing extracts of grasses, Der p, P, Alt a, Fel d 1, Can f 1 [189]. Employing a panel as shown above, independently of history data, provides a complete skin testing, with possible disclosure of nonapparent sensitizations, which could be subsequently highlighted. Indeed skin positivity to different allergens can be ascertained about 2–3 years before the specific symptoms. The inclusion of Fel d 1 is imperative because it is found throughout the world, even when no contact is manifest (Chap. 5). The clinically important pollens vary according to location, so it is best to refer to the pollens prevalent in the region or country: some patients have been classified as affected with an intrinsic asthma, whereas they could be sensitive to unknown allergens and/or those not included in the common battery of allergens [7]. Another poorly defined aspect is the frequent cross-reaction among pollens, fruits and vegetables, namely, grasses, mugwort and birch with certain antigens in common with apple, wheat, spices, celery, carrot, etc. [111] (Table 1.73), partly explained by profilins and various related plant proteins that may function as cross-reacting allergenic components and therefore could explain that certain allergic patients display IgE-mediated reactions to other pollens as well as distantly related plants. (Table 1.72). A discrepancy may be provoked by certain Fel d 1 extracts that, due to cross-reactivity with Der p, give false-positive tests in cat-allergic patients [8]. In another study, Der p contamination of dog dander

extracts was shown to be the cause of false-positive SPT responses in patients sensitized only to Der p [171]. Such drawbacks can be prevented by using recombinant allergens (RAs) [117, 126, 151] (Tables 1.70, 1.71). Bird allergy is uncommon, often SPTs are positive to Der p contained in the feather bedding material [70], therefore extracts obtained from old feathers may be used.

The ISAAC (International Study of Asthma and Allergy in Children) protocol phase 2 module 3.2 includes the following aeroallergens: Der p and Der f, cat hair, mixed grasses [Dac g, Lol p, Festuca pratensis (Fes p), Poa p, Phl p, and Avena elatior], Alt a, mixed trees (Alnus glutinosa, Betula verrucosa and Corylus avellana). This protocol is specifically intended to allow comparisons between centers [143].

For the diagnosis of FA, one should proceed on the basis of (1) epidemiological data (foods more regularly consumed in a typical Mediterranean diet for infants are CM, egg, wheat); (2) age: in an infant aged ≤ 6 months on an exclusive CM diet, the related proteins should be tested (Table 1.75), subsequently egg (two allergens), cereals, wheat, cod, peanuts, nuts, etc., adding bovine seroalbumin (BSA) if meat allergy is suspected; (3) history, recalling that alimentary customs influence the frequency of allergic sensitizations. In addition, children who are monosensitive to grass pollens may show an unusual prevalence of positive SPTs to food allergens (Chap. 9). We always perform SPTs to foods and inhalants in the same session; for fruits and vegetables see “Prick + Prick Testing.”

Extracts to Be Employed

The principal obstacle is the inadequacy of extract characterization, purification and standardization, from which both qualitative and quantitative differences often originate, since the extracts produced vary considerably as extraction techniques are generally different, thus affecting SPT optimal potency and reproducibility

(Chap. 1). A basic prerequisite of SPT reliability is biological extract standardization [128]. Although the number of RAs continues to increase (Table 1.70), at present several RAs related to food allergens are available. In addition, the digestion role in modifying food antigenic properties should be better defined. Gad c 1 is the most purified food allergen and hence the most reliable (Table 1.74), followed by peanuts, CM and egg. SPT sensitivity for codfish is 100%, for egg 70%, and for peanut it ranges from 45% to 100% [121]. Cereals yield highly specific responses from a biochemical point of view. However, there is no clinical correspondence, as we have demonstrated for chocolate, thus explaining why when employing commercial extracts from different producers to investigate the same group of patients, results can be very divergent and yield unexpected (false) negative results. Several of the above problems will be obviously unraveled using RAs: use of a single RA can play an effective role as a marker of severe atopy, delivering a useful means to individuate child sensitivity to a given allergen [117, 126]. The concentration usually utilized in conventional extracts (1,500–10,000 BU/ml) was shown as the most fitting to elicit a specific response without aspecific irritating reactions, being effective even when falling to 3,000 BU/ml [107].

Choice of Lancets

Presently, utilizing single-use lancets has gained popularity, especially if allergenic extracts coat the point (Prilotest): they are easy to use, prevent excessive traumas and provide homogeneous and reproducible results, in addition to assuring a more accurate standardization, but they are expensive. Table 6.7 [47, 105] summarizes the features of different devices in use: the Morrow-Brown needle has a new version [47] and the Duo Tip Test has a bifurcated needle [105]. Commonly used lancets such as the ALK lancet (module 3.2) are manufactured in such a way as to allow a small point to penetrate 1 mm into the skin with a collar or flare on the

Table 6.7. Characteristics of the different lancets available for skin prick tests

Name	Pricker	Stallerpoint	Allerprick	M-B	Duo Tip Test
Firm	D-H-S	Stallergènes	HAL		Lincoln
Technical data					
Needle tip (mm)	1	1	2	1	2.5
Total length (cm)	3	3	10	3	4
Diameter (cm)	5	2.8	3	3	
Material	Metal	Plastic	Plastic	Plastic	Plastic

Pricker: D-H-S, Dome-Hollister-Stier, Spokane, WA; Stallerpoint: Stallergènes Laboratoires, Fresnes, France; Allerprick: HAL, Hall Allergen Laboratories, Haarlem, Holland; M-B: Morrow-Brown needle, Lincoln Diagnostics, Decatur, IL. ALK, Allergologisk Laboratorium A/S (Hørsholm, Denmark).

Data from [47, 105].

instrument to prevent further penetration of the point, also producing more consistent results. Shorter points are problematic in that they produce false-positive tests, while longer points are discouraged in infancy because they induce visible bleeding. In practice, either insulin needles or single-use 25- to 26-gauge hypodermic needles can also be used, both to be discarded after each test [120].

The present version of the MultiTest (MultiTest II) is a multipuncture applicator with eight heads loaded with seven antigens and glycerin as negative control. The heads, 1.9 mm in length, are grouped in two rows of four. It is also suggested for use in infants with different preparations [131]. In 72 Estonian 4- to 6-year-olds [71] and in older children [15], it appears to be exact and reproducible, except for drawbacks due to an excessive test proximity (each head is separated by 2 cm, and the two rows are separated by 3 cm). It seems to be suitable as a screening test with several major allergens [15], similarly to the Quintest, a five-headed device [105].

Testing Methods

Before Execution

- Check whether the child has previously shown severe and/or anaphylactic reactions to the allergen to be tested; in particularly sensitive children and when AD lesions are extended, it is wise to revert directly to an *in vitro* test.
- Investigate whether the children referred have withheld medications that could influence their response to SPTs [30]. The following withholding periods apply: for hydroxyzine and clemastine, 2–4 days; cyproheptadine, diphenhydramine, chlorpheniramine, promethazine and all short-acting antihistamines (acrivastine, azelastine, cetirizine, fexofenadine, levocabastine, levocetizine, loratadine, oxatomide) and ketotifen, 7 days; theophylline 24–48 h. There is no need to discontinue inhaled short-acting bronchodilators and cromolyn or nedocromil sodium and inhaled corticosteroids (CSs). Oral CSs may interfere with late-phase hypersensitivity reactions only if administered for more than 1 week, whereas application of high-potency topical CSs should be discouraged [95].

Execution Technique

- Adequate skin cleaning can be accomplished by an ether-soaked cotton-wool wad to remove the grease from the skin, so facilitating the permanence of allergenic extracts at the site of application.
- Mark the skin with a ball-point pen for the allergens to be tested.

- Apply a small drop of each test extract to the skin of the volar forearm.
 - Drops are placed about 5 cm from the wrist and about 3 cm distal to the elbow crease (reduced measures in younger children).
 - Direct the sterile lancet through the allergen droplet, at an angle of 60° to the skin surface to reduce the variable pressure exerted by the investigator's hand.
 - The puncture should be moderate to avoid unnecessary bleeding as well as false-positive tests, and lancets preloaded with allergen should remain in the skin for 1 s.
 - When testing a battery of allergens, perform the tests in parallel lines placing the drops about 2–3 cm apart, occasionally using the left forearm, always discarding the lancet on completion of each test to avoid mixing allergens [95].
 - Perform a positive control with histamine hydrochloride, 1 mg/ml [49] always approximately 4 cm away from other tests, otherwise histamine can infiltrate the area of other tests, giving questionable results [80] and then a negative control (normal saline, 0.9%). For children aged 9 years, 10 mg/ml histamine has been suggested [143]. Both controls must be applied in the same fashion and at the same distance as all the other tests [165]. Alternatively one can place one at the beginning and one at the end of the test battery.
 - Gently wipe away the excess solution with a paper tissue (different for each test) approximately 1 min later, avoiding smearing of test solutions to adjacent test sites: this operation does not interfere with the intensity of skin response.
 - Extracts should be kept refrigerated at 40°C.
- Especially in infancy, a laser technique is advisable instead of puncture testing, insuring a greater reliability and reproducibility, but with a disadvantage that cannot be overlooked: its high cost [75].

SPTs for allergy diagnosis should be performed in duplicate and quadruplicate for research purposes [59].

Scoring System

SPTs are read within 15–20 min in a standard manner. The size of skin reactions is related to the size of the histamine wheal resulting from the positive control (diameter, at least 3 mm) considered.

We no longer use the scoring system of Aas and Belin [1] and consider positive only children with a ≥ 3 -mm wheal (equal or twice the size of the histamine wheal) with an area of $\approx 7 \text{ mm}^2$ (cut-off), to record the highest percentage of positivities [128]; if smaller (2 mm) it renders any evaluation difficult and does not warrant the trauma caused by testing [49]. The difference between 2 and 3 mm in mean diameter is equivalent to a tenfold difference in skin sensitivity, an important factor in epidemiological studies [59].

Cut-off values have been recently evaluated as follows (mean diameter/surface of wheal): CM 5 mm/29 mm², egg 4 mm/16 mm², wheat 3 mm/7 mm², peanut 6 mm/40 mm², soy 3 mm/9 mm², with significant differences in wheal size between children allergic or tolerant to the above foods, except for soy (NS) [52].

The method of comparing SPT responses with controls ensures the greatest reliability and reproducibility, also balancing the operator bias [98]. Studies that do not conform to this universal grading system (Table 5.1) make any evaluation and reproducibility of data difficult [98]. SPT dimensions were analyzed, for example, by Sears et al, who noted that the highest prevalence of asthma corresponded to a diameter >8 mm (Chap. 11), and Hill et al suggest that a response of 4+ is equivalent to a positive FCT [66]. More precisely, this equivalence is seen when skin wheal diameter is greater than a given size, that is CM, 8 mm; egg, 7 mm; and peanut, 8 mm; smaller in children aged <2 years: 6, 5, and 4 mm, respectively [160]. Especially with food and inhalant allergens and in very sensitive children, we see wheal diameters >1–2 cm, more with the erythema with food allergens and with inhalants, also 2–5-fold greater than the histamine wheal.

Evaluations are carried out and made more precise in three ways:

1. Calculating (in parallel with controls) the mean wheal diameter, by adding or multiplying the largest diameters and calculating their mean; however, since the reactions can be oval or irregular in shape, the largest and smallest wheal diameters are measured, added and divided by 2, to obtain the mean wheal diameter.
2. With a transparent millimeter ruler or one equipped with holes coinciding with increasing diameters (1, 2, 3, 4, 5 mm, etc.) to determine the wheal diameter and erythema diameter.
3. Using a computerized program with a tablet and a digitizer pen to very precisely outline the wheal on transparent paper; subsequently the SPT scanner calculates SPT areas [133].

Positive and negative controls should always be included:

- A positive control is extremely helpful to compare various responses, check the technique's reliability and exclude the inhibition of skin reactions possibly caused by a concurrent treatment.
- A negative control can reveal a likely aspecific skin hyperreactivity, as a marked red dermographism occurs in some children following the puncture micro-trauma.
- A doubtful reaction due to wheal dimensions can be considered as negative in the presence of a great histamine reaction.
- Generally a smaller histamine dilution would be preferable, thus ensuring better reproducibility, inducing wheals which facilitate both comparison and differentiation between negative and positive responses [185].

Table 6.8. Mean value (cm) of the wheal induced by histamine according to age

Age (months)	Histamine	
	1 mg/ml	10 mg/ml
0–3	0.77±0.75	1.90±0.92
3–6	1.07±0.58	3.07±0.88
6–12	1.67±0.69	3.40±1.18
12–24	2.23±1.14	3.29±0.86
Adult	2.48±1.0	4.75±1.11

Data from [99].

Failure to respond to a positive control suggests that there is some interference with SPTs, such as parents failing to discontinue antihistamine drugs before testing [120]; one should consider such an occurrence and repeat the tests at the subsequent control visit.

Several investigators have considered the end-point titers as the extract progressive dilution giving a wheal size of 3 mm or a wheal size similar to that of the histamine-positive control [37].

IgE-mediated reactions appear within 1–2 h occasionally followed after 4–6 h by a delayed-type hypersensitivity (DTH) resolving in the subsequent 24–48 h. Possible systemic reactions, however exceptional, should not be underrated: thus it is recommended that SPTs are done directly by pediatricians or under their personal supervision [37].

- After SPTs are done, children should be supervised by pediatricians in the office/hospital for at least 20 min, the reading interval, as for SIT (specific immunotherapy), or longer for high-risk children [49].
- In children aged a few months to 2 years, positive control response (1 mg/ml) until 12 months is always <3 mm, as Table 6.8 [99] shows. If doubt arises with an 1-mg/ml dilution, it is advisable to repeat the test with a 10-mg/ml dilution [99]. Even in children aged 5–25 months, the control diameter is not significantly related to age: the 1.8±1 mm mean diameter (histamine 1 mg/ml) is <2 mm in children aged <12 months [45]. The popular notion that infants cannot be tested stems from the idea that they rarely produce detectable sIgE levels; however, we have seen infants with positive test results, including a 6-month-old girl with a 1 × 1-cm response to egg white.

Evaluations

One point should be clear: SPTs measure reactions to antigen-specific IgE; however, SPTs are not diagnostic, since a positive SPT alone does not indicate a definite clinical sensitivity to a given allergen, so it is necessary to analyze any response thoughtfully, case by case, con-

Table 6.9. Sensitivity, specificity and positive predictive value of SPTs, total IgE and PP in infants aged 6–18 months

Parameters (%)	SPTs		Total IgE		PP	
	6	18	6	18	6	18
Sensitivity	22	40	44	63	22	40
Specificity	100	100	70	55	100	95
Predictive value +	100	100	38	43	100	80

Data from [91].
PP Phadiatop Paediatric, SPTs Skin prick tests.

sidering history data. A puzzling test should be repeated and/or confirmed before making a decision, recurring to FCT or BPT (bronchial provocation test) if foods or inhalant allergens, respectively, are concerned.

During recent years, SPT-negative results have been the subject of intense discussion: it has been recently confirmed that if children with suspected FA present properly performed negative SPTs for one or more incriminated foods it would make an IgE-mediated FA very unlikely. These children might be better diagnosed by searching the allergens to which they may be sensitive. We have demonstrated that FCTs were positive in 7 out of 35 children with AD and negative SPTs to CM; therefore a method with a 20% ineffectiveness cannot be considered as fully reliable. In a recent study, 74% of diagnoses made with SPTs were not confirmed by FCTs [25]. In cases of rhinitis or conjunctivitis with a history highly indicative of allergic disease, SPTs can be negative since sensitizations are localized to the target organ;

thus we suggest a nasal provocation test (NPT) and/or a conjunctival provocation test (CPT) (see “Provocation Tests”).

Recently the SPT characteristics were evaluated at the cutoff level of 3 mm: CM hat 0.72 sensitivity and 0.62 specificity, and α -lactoglobulin (ALA) 0.66 and 0.64, β -LG 0.84 and 0.53, casein 0.55 and 0.87, respectively; PPV (positive predictive value) was highest for casein (0.78) and NPV (negative predictive value) highest for β -LG (0.81) [56]; see also Table 6.9 [91]. In general, SPTs (and RAST/CAP) for more standardized allergens (peanut, fish and egg white) are the most reliable, especially with immediate reactions to foods [149].

Prick + Prick Testing

P+P is a technique first employed in 1978 (Table 6.10) [33, 48], because fresh fruits and vegetables have extremely labile allergens that cannot be preserved. Therefore, for diagnostic purposes, it is preferable to employ fresh foods instead of commercial allergenic extracts, as using fresh material without preservatives such as glycerol is particularly suitable [48]. Some fruits contain vasoactive substances able to produce false-positive results. Foods should be fresh and not frozen since storing them at -16 °C causes some food proteins to lose their allergenic qualities; furthermore, several substances lose their allergenicity within 48 h [63]. The P+P technique is also very worthwhile when commercial extracts are not at hand, for example, exotic fruits, or when allergens are denatured to produce extracts and for a direct diagnosis of latex allergy.

Table 6.10. Studies done with the P+P method

Authors	Year	Fresh foods tested
Hannuksela and Lahti	1978	Apple, carrot, potato
Andersen et al	1978	Apple, potato
Dreborg and Foucard	1983	Apple, carrot, potato
Pastorello	1985	Apple, peach, plum, pear, cherry, apricot, banana
Ispano et al	1985	Apple, onion, tomato
Sacerdoti et al	1987	Wheat, egg, CM, chocolate, fish, tomato, etc.
D’Urso	1987	CM, egg, fish
De Martino et al	1988	Apple, peach, tomato, pear, egg, CM
Ortolani et al	1988–1989	Apple, peach, apricot, tomato, melon
Cantani and Mastrantonio	1990	Banana, apple, carrot, potato, tomato, wheat, egg
Sampson et al	1991	Hydrolysate formula
Ragno et al	1993	3 hydrolysate formulas
deWaard-van der Spek	1998	CM, egg, peanut

Data from [33, 48]
CM cow’s milk.

Table 6.11. Reliability of P+P technique and RAST in the diagnosis of 3 HFs in 20 children with CMA

	NIDINA HA		ALIMENTUM		PROFYLAC	
	P+P	RAST	P+P	RAST	P+P	RAST
Specificity	0.69	0.22	0.89	0.89	0.80	0.63
Sensitivity	0.63	0.50	1	1	0	0
Predictive value +	0.62	0.34	0.62	0.50	0	0
Predictive value –	0.70	0.35	1	1	0.82	0.72

Data from [136].
P+P prick + prick.

Indications

We have successfully employed P+P with several foods, including CM, egg, wheat, the most common foods of children’s diet and frequently suggested as inducing FA even by the 1st year of life, and several fresh fruits and vegetables, demonstrating P+P’s greater reliability compared to commercial extracts disk. In addition to being easily arranged, P+P could be a safe and useful diagnostic method (Table 6.10). Applying the analytical reliability criteria for CM, egg and wheat, we have found a lower sensitivity for CM and wheat, and a higher effectiveness compared to SPTs. The P+P technique applied to hydrolysate formulas (HF) has shown good diagnostic reliability (Table 6.11) [136]. The high P+P PPV and NPV supports the use of this simple and noninvasive method before prescribing HF to babies with CM allergy (CMA) [136]. P+Ps gave unexpected results in a 9-month-old girl with severe CMA seen by us who had negative SPTs for CM. By performing P+P tests with

CM diluted 1:1 with saline there was a wheal 1-cm-large-plus a 2-cm-large erythema (see also in Chap. 9). Similarly, this technique is specifically applicable to pollen-allergic babies with OAS [48].

Techniques

The technique is very simple. One pricks a normal, sterile lancet into a fresh food, assuming that it is solid, and immediately thereafter into the skin, as when doing an SPT [48]. When testing liquid foods such as CM and egg, one dips the lancet directly into the food. With other foods, including wheat, a mixture of flour and boiled water can be prepared [33] (Figs. 6.20, 6.21); similarly, HF formulas were diluted fresh according to the instructions on the can, as for a normal preparation [136]. As regards latex, one can perform puncture skin testing with latex gloves, obtaining positive results in 70 % of cases [114].

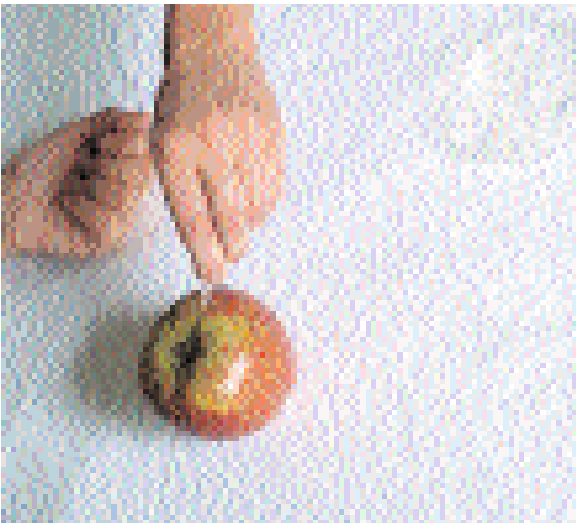


Fig. 6.20. Prick-by-prick method (for details see text)



Fig. 6.21. Prick-by-prick method (for details see text)

Patch Test or Epicutaneous Test

The PT (patch test) is the diagnostic tool of choice for ACD and selected AD cases. The significant correlation with total and specific IgE suggests a prominent IgE role in the reaction mechanisms, mirroring the sensitization process [84].

Indications

PTs confirm an ACD suspected case, recognize a sensitizing substance among many suspected ones, bring out the relevant but unsuspected substances, mainly in doubtful cases, and establish which materials can be tolerated by patients without risk, above all when very sensitive [16]. Because PT can aggravate an acute and disseminated dermatitis, or elicit an unspecific response in correspondence with the application site, it is wise to postpone testing to a later date until the lesions improve [153]. However, the risk of applying a standard panel is insignificant compared to the wealth of the information obtained [53].

Techniques

PT consists in placing the test material, usually commercial substances or extemporaneously prepared by specialists, in a proper vehicle and an adequate concentration is applied under occlusion on the child's upper back for 48 h. The ICDRG (International Contact Dermatitis Research Group) [16] and the NACDG (North American Contact Dermatitis Group) [95] have published lists of allergens for PTs, establishing pertinent concentrations and indicating application methods:

- Prefer the upper back skin, examining the area and excluding zones with minimal evidence of lesions [84], putting off testing if lesions are acute or disseminated. Applications on healthy skin yield positive results in 87% of cases [153].
- Mark the outline of test sites with a spotlight fluorescent pen. Children should remain still during testing to avoid skin folds or streaking.
- Commonly available standardized test material varies according to the occlusive patches employed, requiring dilution to be nonirritating under patch conditions. The test substance is classically applied to 1 cm² of soft fabric under occlusion by an impermeable substance and subsequently applied to the skin with nonallergenic Blenderm tape.
- Test material is mounted on cellulose acetate and coated on a water-impermeable sheet of polyester covered with a protective sheet of polyethylene, and packed into a pouch of laminated foil made of Al, polyethylene, and polyester.

- Draw map of PT location on PT form.
- Inform patients that test sites should remain dry until removed. However, they should be immediately removed if severe itching, a burning sensation, or irritation occurs.
- Remove test 48–72 h [53] or 24 and 48 h [84], or 24 h for foods, after application [119]. Reading is done after at least 30 min (mostly after 1 h), so that a possible irritation produced by adhesive tape is reduced, making a delayed reading at 24 h [16, 53].

In children, the employment of Finn chambers is more practical and less invasive. These chambers are formed by small Al cups with an 8- to 12-mm diameter, a 50-mm² surface and a 20-ml volume, applied to the skin on nonallergenic tape (Scampor). The test substances, when incorporated in semisolid supports, can be directly applied to the small cups, when liquid a small disk of filter paper placed in the chamber is saturated by the test substance [37]. Another method, the TRUE test, consists of a mixture of 20 allergens incorporated in hydrophilic gels, coated on a water-impermeable sheet of polyester and dried to a thin film; the film once applied to the skin is hydrated by skin perspiration and releases the allergen; the high accuracy of the whole system and allergen distribution on a 9×9-cm polyethylene support provide a homogeneous allergen bioavailability [37, 53, 95]. The allergen material at hand is widely available, but you do not find it everywhere, thus test utility is limited to routine investigations [16].

The Rapid Patch Test is similar and includes three panels with a total of 30 allergens. Epiguick consists of 20 allergens on Finn chambers mounted on Scanpor tape. In children aged <4 years with AD and ACD, it is suggested to do a SAFT (skin application food test) to study food and contact allergens applied on uninvolved skin in a 0.5-cm² small cup [119]. Since children with AD are probably more likely to have irritant or false-positive reactions to metals, a shortened standard PT series for pediatric patients has been proposed [145].

To patch test latex, test latex hapten by means of specific extracts or apply a latex glove fragment on the upper back, to be read after 48–72 h [114].

The latex exposure test is required for a convincing diagnosis. In the test used, the child's wet hands are exposed to a wet rubber latex glove finger for 15 min, and if there is no reaction the whole hand is exposed to the whole glove for 30 min; vinyl or Tactylon gloves are used on the other hand as control [114].

Recently, the PT with foods (PTF), such as the atopy patch test (APT), has been introduced as a procedure enabling the identification of AD children reacting with AD worsening to the administration of the offending food [110], as well as reducing the need for OFC in these children [142]. In the case of peanuts, for the preparation of the PT material, peanuts were whipped and a

mixture was made with one part of petrolatum and two parts of peanuts: 20 mg of this material was applied to the uninvolved skin of the back using Finn chambers and Scanpor tape as above. The suggested occlusion time is 72 h and the results are read 30–60 min after removal. SPTs were positive in 16 patients (12%), whereas PTs for foods proved positive in 25 (19%) and a positive challenge was observed in 12 subjects (9%) [152]. For CM, egg, wheat, and rye, APT sensitivity was 60%–93% and specificity was 71%–97%. The SPT corresponding figures were 13%–41% and 97%–99% [162]. In infants with CMA the APT had a sensitivity of 79% and a specificity of 91% [44]. The recent ready-to-use APT had 79% sensitivity vs 44% of the APT, a similar specificity (93.8%) and a test accuracy of 82.9% vs 63.4% [74].

Evaluation of Patch Test Reactions

Evaluation of PT reactions can be based on ICDRG guidelines:

- 0 No skin change compared to controls
- 1 Weak positive, nonconfluent erythema and discrete papules
- 2 Strong positive, confluent erythema, papules, vesicles
- 3 Severe positive, redness plus blistering [53]
 - or based on the following scale [152]:
 - 1 Erythema and edema
 - 2 Erythema, edema, and few papules
 - 3 Erythema, edema, and papules covering most of the patch test area
 - 4 Erythema, edema, and papules spreading outside the patch test area or vesicles

Frequency of positivities greatly decreases from infancy to adulthood, as seen in a Der p study: 1–5 years, 60%; 6–10 years, 76%; 11–15 years, 50%; 16–20 years, 21%; 21–25 years, 29% [153]. Especially in AD children it is suggested that the cells infiltrating the PT site be studied with suitable techniques [153].

Photopatch Testing

A PT variant used for the diagnosis of photodermatitis is done by applying the suspected allergen on the skin in duplicate; after 24 h one of the tested skin sites is exposed to sunlight (10 min in summer, 30 min in winter). After 48 h the diagnosis is made with the same PT modalities [16]. Alternatively, artificial light sources can be adequate and provide enough of the long-wave ultraviolet light A (UVA) [95].

In vitro Immunoallergic Tests

Total Serum IgE

In allergy diagnosis, assay of total serum IgE levels (PRIST, paper radioimmunosorbent test) can play a significant role, taking into account the potential lack of correlation with the child's clinical state.

Indications

PRIST measurement has some definite indications:

- At birth, in cord blood as a predictive method of allergy (see Chap. 3)
- At every age as a mass screening
- To correctly classify allergic and nonallergic children
- In wheezing children
- To confirm an AD or FA diagnosis [27]

Total IgE Level Determination

The most commonly employed assays to measure total serum IgE levels (or other biological specimens) are:

- Radioimmunologic assay (RIA): the most classic is the Pharmacia PRIST, which measures anti-IgE antibodies covalently attached to a solid phase such as a paper disk, or a plastic microtiter well is incubated with an appropriate dilution of the serum or other biological liquid. A complex of anti-IgE-IgE antibodies is formed and by adding anti-IgE marked with I^{125} a new complex of anti-IgE antibodies–anti-IgE-marked antibodies is formed and directly measured.
- Immunoenzymatic assay (EIA, enzyme immunoassay, ELISA, enzyme-linked immunosorbent assay, and Instant ELISA), employing enzymes such as alkaline phosphatase and peroxidase as a detector system, instead of a radioisotope. The unit of measure used is the kilo-unit $\times$ l (ku/l) or the International Unit $\times$ ml (IU/ml).

An IgE assay in stools was also proposed as a noninvasive and economic indicator of food sensitization [5].

Total serum IgE values in healthy children according to their age are shown in Tables 6.12 and 6.13 [76, 82]. A study on 1,160 newborns determined IgE levels at 1, 2, 3, 5, and 6 years of age and the data were compared with the original population-based sample of 4,082 children [82]. Data given in ku/l (1 U/ml=1 ku/l) [82] are more widespread than the GM data [76]. Statistically significant higher total IgE values were found in boys than in girls at each age; this sex difference was not statistically significant within the group of atopic children [82]. IgE levels absent or very low at birth subsequently increase compared with the rise and sum of single sensitizations,

Table 6.12. Normal values of total IgE (UI/ml)

Age levels	GM	Limits	GM ± 2 SD
Birth	0.22	<0.1–1.5	0.04–1.28
6 weeks	0.69	<0.1–2.8	0.08–6.12
3 months	0.82	0.3–3.1	0.18–3.76
6 months	2.68	0.9–28	0.44–16.25
9 months	2.36	0.7–8.1	0.76–7.31
12 months	3.49	1.1–10.2	0.80–15.22
2 years	3.03	1.1–49	0.31–29.48
3 years	1.80	0.6–7.6	0.19–16.86
4 years	8.58	2.4–34.8	1.07–68.86
7 years	12.89	1.6–60	1.03–161.32
10 years	23.66	0.3–215	0.98–570.61
14 years	20.07	1.9–159	2.06–195.18

Data from [76].
GM geometric mean.

Table 6.13. Normal values of total IgE (UI/ml)

Boys					
Age (years)	1	2	3	5	6
Percentiles					
25	2.5	6	9	18	18
50	6	19	25	45	47
75	16	58	72	110	118
90	44	137	197	271	269
95	85	248	297	501	493
Girls					
Age (years)	1	2	3	5	6
Percentiles					
25	2.2	4	7	11	12
50	4	12	16	25	32
75	11	3051	64	80	
90	55	77	116	155	249
95	62	189	206	241	421

Data from [82].

in turn dependent on genetic and acquired factors, but above all correlated with the extent and persistence of contact and the antigenic stimulus (Fig. 6.22).

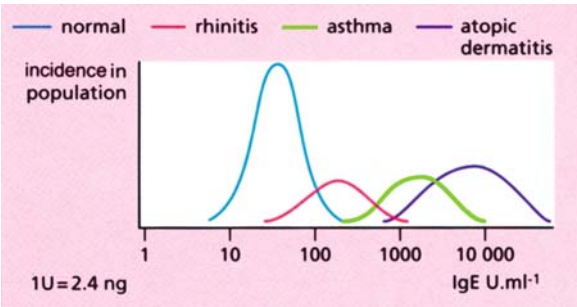


Fig. 6.22. IgE levels in allergic disease. Determination of total IgE serum and cord blood is of some value in allergy diagnosis, even if there is a great overlap between normal and allergic children. In general, however, the more severe the IgE inflammation, the higher the serum IgE

Total IgE Level Determination in Neonates and Infants

Total serum IgE levels in these early ages are nearly always less than 0.02 UI/ml (Fig. 2.10). Since the greater part of assays allows measurements from 0.5–10 UI/ml, it is indispensable to use ultrasensitive assays, that is, RIA (Pharmacia IgE RIA Ultra 50) or ELISA (Pharmacia IgE EIA Ultra 50). Values of >1 UI/ml at birth, >5 UI/ml at 1–3 months and >10 UI/ml at 4–6 months are suggested as probably pathological [127].

Advantages and Disadvantages

As regards predictive values, PRIST has an uncertain clinical significance at birth (Chap. 3), but is a useful tool to identify atopic disease early, before clinical symptoms are evident in children previously manifesting severe reactions, anaphylactic shock or severe AD, and for research purposes in prospective studies aimed at atopy prevention [27]. Total IgE associated with sIgE for Der p and egg white in 6-month-old infants are predictive of a conversion to sIgE values positive for Der p at 5 years, resulting in a reliable screening method [150]. In addition, we have reported valuable results in children with bronchiolitis, CNO, OME and hyper-IgE syndrome [27]. In children, especially preschool children, such an assay could have a diagnostic value significantly higher than in adults [32]. However, the diagnostic value of PRIST in pediatrics also has disadvantages, as Table 6.9 summarizes, such as low levels in subjects definitely allergic [120], high IgE levels in nonallergic diseases and in nonatopic children and conversely normal IgE levels in some atopic children [69].

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