Atopic Eczema in Infants

6

Alain Taïeb, Franck Boralevi

6.1 Introduction

Atopic eczema/dermatitis in infancy is both the earliest manifestation of atopic disease and the period in life when the disease reaches peak incidence rates. This common disease has not been taken very seriously because it has traditionally has a benign reputation and has even been considered as a sign of good health. More recently, based on data from pulmonologists and allergists, pediatricians would rather consider infantile eczema simply as a risk factor for asthma, a disease with a far worse reputation. Physicians have long been reluctant to treat, with the obscure fear of triggering distant serious "metastatic" disease [14], reminiscent of the ancient humoral theories regarding eczema as nature's way of eliminating toxic principles. Modern topical steroid phobia, which is common in Japan and exists on a more modest scale in other parts of the world such as the UK [8], is probably a transcultural sequel to this traditional way of thinking. At the beginning of the twentieth century, infantile eczema remains a global enigma but can serve to investigate and understand the pathophysiology of atopic eczema and probably even the natural history of other atopic diseases.

6.2 Infantile Eczema: What It Is and What It Is Not

In the galaxy of "eczematology" (a word coined by Besnier [3]), eczema in infancy is not a new disease and was recognized as a common disorder 100 years ago (5 %–10 % of infants according to Besnier quoting Marfan [3]). Infants probably affected with our modern atopic eczema can be traced back to ancient and classic times well before the actual birth of clinical medicine at the end of the eighteenth century. Descriptions of cutaneous catarrh with predominant facial and scalp involvement associated with itching and sleeplessness but overall good general health can be found under various headings in several languages, underlining the difficulties in classification. These include achor, scabies capitis simplex (Plenck), strophulus, darters, *gourme*, porrigo larvalis or mask-like porrigo (Willan-Bateman), tinea mucosa (Alibert), *Kopfrande*, tinea lactea, *Milchgrind*, crusta lactea, *croûtes de lait*, milk scalp, etc. The category of infantile eczema already in use in the medical nosography at the end of the nineteenth century has, however, probably been heterogeneous from the outset, and this matter has never been satisfactorily clarified, particularly because it is difficult to classify mild cases, and because there may be overlap between the so-called seborrheic eczema of the face and scalp (cradle cap), as defined by Unna, from true infantile eczema, if this distinction holds true. An important paper was published in 1909 by Adamson, a British dermatologist heading the Paddington Green Children's Hospital in London, who clearly delineated seborrhoic dermatitis of infancy with its typical bipolar rash (Fig. 6.1) from infantile eczema (Adamson, 1909) and recognized that the same disease was also described in Bordeaux at the Children's Hospital by Moussous, a professor of pediatrics who had a keen interest in dermatology [27] and his student Lebard who wrote a thesis on the subject in 1905 [26], but interpreted it differently as eczema. Adamson makes the following point: "Eczema in nurslings is an eruption affecting essentially the scalp and face … it has a characteristic mask-like distribution on the forehead and cheeks, leaving free the mouth, nose and orbits. It is markedly pruritic, it is a weeping eruption, it is made worse by the least local irritation, it is very intractable, and does not clear up rapidly with mild antiseptic

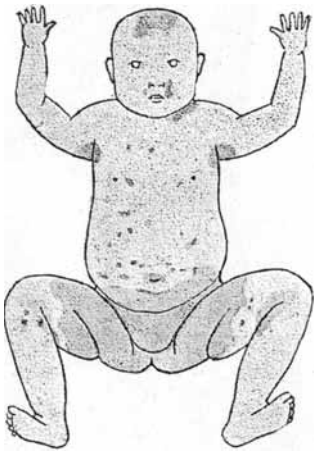


Fig. 6.1. Distribution of lesions in infantile seborrheic dermatitis (From [1], with permission)

applications as does the seborrhoic dermatitis, and it does not affect the napkin region." Adamson notes, however, that infantile seborrhoic dermatitis (ISD) clears in a few weeks with a daily bath containing boric acid and a sulfur ointment. He suggests that ISD has a parasitic (the term used in that time encompassing all microbial acquired diseases) origin, a theory that has been followed until recent years with studies on the microflora of ISD showing the presence of *Malassezia* yeasts associated with staphylococci and its treatment with topical imidazoles [40].

6.3 Historical Background: Hall's Thesis (1905)

The conceptions and classifications of infantile eczema have been reviewed extensively in the Cambridge M.D. thesis written by Arthur Hall, a physician in Sheffield, who probably performed the first scientific study on the subject [17]. Table 6.1 gives an overview of the divisions defined by Brocq [6], a noted contemporary theorist of Hall in dermatology, which underlines already major differences in natural history, although based more on intuition and clinical experience than on evidence-based medicine.

Concerning etiologic theories, according to Hall, three groups emerged (before the allergy era), namely digestive disturbance, external irritation, and a third miscellaneous group including vaccination, dentition, and diathesis. Digestive disturbance, whatever its exact nature, was the majority opinion. Hebra had led the group of supporters of the irritant theory, followed by Unna, who adhered to the importance given to microorganisms, and several prominent authors who combined the two theories of digestive disturbance and external irritation. Based on the rigorous prospective study of 60 cases of infantile eczema, Hall concluded that dentition and vaccination were irrelevant, that an inherited diathesis ("in the loose sense in which that term was used") was not supported (but he did not

Table 6.1. Louis Brocq's subsets of infantile eczema (1903), based on clinical observations, tend to isolate two benign outcome forms and two protracted/severe forms (modified from [17])

	Early benign non seborrheic	Benign ISD type	Severe	Eczema-asthma
Age at onset	2–8 months	4–8 months	4–8 months	4–8 months
Areas involved	Face first (cheeks, forehead, temples), later buttocks, limbs (extensor), trunk if severe	Scalp, ears, nasolabial, mouth, neck, anal fold, groins, articular folds	Legs (severe), face and arms (milder)	Not described
Clinical aspect	Minute vesicles on erythematous base (*eczéma vésiculeux vulgaire*), successive crops, irritable; lichenification	Red areas, often nearly dry and squamous or moist, oozing; "eczematized seborrheid"	Urticarial papulovesicular spots run together and form sheets, with true vesicular eczema on top; lichenification	Intense itching followed by vesicular eczema; lichenification
Associated conditions	Diet problems, neurotic parents	Fat, overfed, much improved by proper diet and local treatment	Parental Arthritis, neurotic intoxications (tea), lymphatism tuberculosis, syphilis	Alternate bronchitis or asthma
Duration	Until 15 or 24 months old	Does not persist after infancy	Throughout life or until later childhood	3rd–10th year

have the opportunity to examine the fathers), and that the digestive disturbance or malassimilation theory had strong arguments against it, namely no digestive symptoms associated with eruption (preceding or accompanying it); no specific association with malnutrition or rickets; most patients were breast-fed alone and in most cases the mothers had breast-fed previous children under similar conditions who did not suffer from eczema; there was no evidence of overly frequent pregnancies, overextended breast-feeding, or illness in the mother; and few cases occurred in the summer months when gastrointestinal disturbances are the most common. On the other hand, there were strong arguments in favor of external irritation, i.e., beginning on exposed areas (head); other (distal) eruptions less severe and tending to disappear when the original site recovered; constant age at which the eruption appeared (corresponding to the time when the infant was released from the extreme protection received during the first few weeks of life); and the greatly increased percentage of cases that began in the colder months of the year (Fig. 6.2). This paper is very interesting to read today, and some of its conclusions were reached again recently (without being aware of its existence), combined with a discussion of the modern allergic view by the senior author of this chapter [38]. We would like to quote a few excerpts from the illuminating discussion of Hall's data. "There are certain surrounding conditions present in infancy, which cease, as infancy emerges into childhood. These are necessary accompaniments of this period of life … just as likely to produce irritation of the skin as those conditions of various kinds to which persons are exposed in adult life, and which we call 'occupation or traumatic eczema.' … Most cases of infantile eczema are, so to speak, the 'occupation eczema of infancy,' and that they usually get well when the occupation (being an infant) is given up … sooner if efficiently treated, but, usually, whether treated or no." Hall reviews the occupation of infancy and notes first "the infant at birth changes from a subtropical aquatic existence to a terrestrial life in a temperate zone. … Its skin makes acquaintance with … irritants, … alkalis (soap), microorganisms, … sweat from the mother's skin, the surface of its clothes … and towels used for drying it," then that "an infant during his first six months of life, has little or no power of localising or removing … these irritants;" he insists on "insufficient drying in cold weather" and notes that the infant has increased primitive skin reflexes, which may contribute to a hypersensitivity to external irritants combined with the impossibility of removing them. Among irritants, he thinks that cold is a predominating factor. Comparing the situation to chapped hands in persons who wash their hands frequently and fail to dry them carefully, infantile eczema "may be termed chapped face." He discusses briefly the role of soot or other atmo-

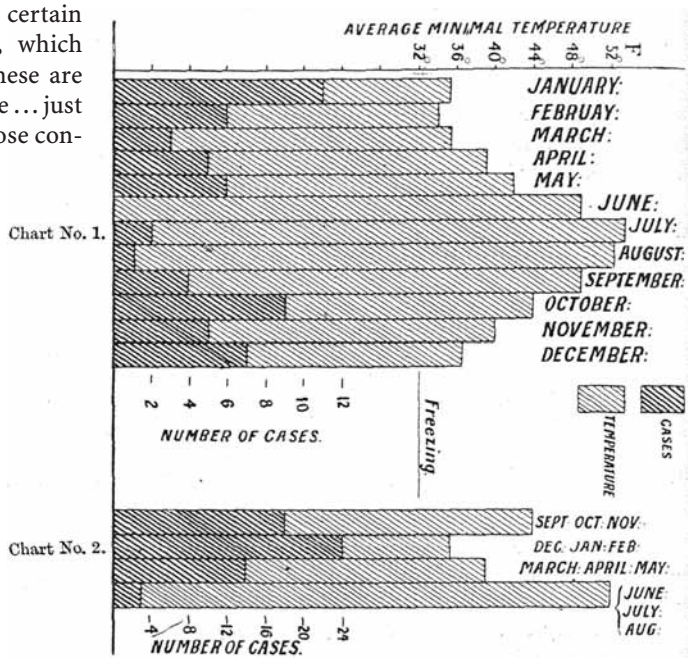


Fig. 6.2. Effect of external temperature on onset of eczema (From [17], with permission)

spheric pollutants and a secondary role for contaminating microorganisms. He concludes more generally, because the infant's disease is considered an experimental model, "I venture to suggest that what is generally called eczema, whether it occurs in infants or adults, is a form of reaction or response of the neurocutaneous apparatus to external irritation… Such a reaction is intended to serve some purpose, possibly to remove the irritant or to protect the skin surface, … a function which, under the present conditions of life … is more detrimental than useful."

6.4 Review of Current Diagnostic Criteria

The classical diagnostic criteria compiled by Hanifin and Rajka [18] and the simpler UK working party (UKWP) criteria, which have now been validated on a large international scale, are not yet fully validated in infants [45]. In the UKWP criteria, the item "onset under age two" is always positive in this age group, but its use does not make much sense for this purpose. The original validation study of the UK Working Party suggests, however, that the criteria can be used in this age group because subgroup analysis demonstrated that the criteria correctly classified most of the children in this age group [46]. In children under the age of 1 year, the UK Working Party recommended that the identification of flexural dermatitis should be modified to include the outer arms or legs in order to separate seborrheic dermatitis of infancy from atopic dermatitis. The data collected prospectively by Fleming et al. [13] to test a postal questionnaire version of the UKWP criteria in infants suggest that the distribution of dermatitis in infancy may be more variable than previously thought. Although typical flexural involvement does not usually develop until about 2 years of age, visible dermatitis was ascertained in this study by mothers and a suitably trained observer on the typical flexural surfaces (e.g., folds of the elbows, behind the knees, fronts of the ankles, around the neck) in proportions similar to the those recorded for the sites believed to be more common in this age group (i.e., cheeks, extensor surfaces of limbs). Over 40 % of the children (15/37) who had visible dermatitis on at least one of the typical flexural sites did not also have dermatitis on their cheeks, arms, or legs. The authors recognize that there is a need to refine the present criteria with a different number of (positive or negative) criteria and maybe even differential weighting of the criteria. This means that Sampson 1990 had already adapted Hanifin and Rajka's criteria to infants (children under 2 years) (Table 6.2). A few remarks are in order here. First, lichenified dermatitis is not a sensitive criterion in very young children, since lichenification generally occurs at the end of the 1st year in Caucasian infants affected with moderate or severe eczema. Second, the minor criteria have not been selected adequately. Scalp involvement is not specific

Table 6.2. Diagnostic criteria for infantile atopic eczema

Modified Hanifin and Rajka's criteria for infants [35]	
Major features	Family history of atopic dermatitis
	Evidence of pruritic dermatitis
	Typical facial or extensor eczematous or lichenified dermatitis
	Diaper area and/or facial mouth/nose area is free of skin lesions
Minor features	Xerosis/ichthyosis/hyperlinear palms
	Periauricular fissures
	Chronic scalp scaling
	Perifollicular accentuation
2003 Criteria for atopic dermatitis in infants adapted from UKWP	
Mandatory feature	Evidence of relapsing itchy skin condition (duration more than 3 weeks)
Other features (3 or more)	Head dermatitis leaving mouth, nose, and orbital skin free
	Pure extensor or mixed extensor/flexor dermatitis
	Absence of diaper area involvement
	Xerosis, diffuse
	Hand eczema
	Skin reactions following food ingestion
	History of atopic disease in a first-degree relative

because it is very common in minor forms of pure seborrheic dermatitis, and ichthyosis vulgaris including hyperlinear palms is difficult or impossible to diagnose clinically before 2 years of age. Perifollicular accentuation is not so straightforward to diagnose, even by a seasoned clinician. A case-control study by Bohme et al. [4] in children less than 2 years of age, examining 29 minor criteria, found that seven minor criteria were met in more than one-fourth of these children, namely xerosis (100 %), course influenced by environmental factors (87 %), facial erythema (54 %), skin reactions provoked by ingested food (39 %), itch when sweating (34 %), positive skin prick test (29 %), and hand eczema (28 %). Since "course influenced by external factor" is particularly vague, facial erythema is redundant with a major feature in infants, prick testing is beyond usual clinical examination, and itch when sweating is not always testable in young children, a modified and simplified set of criteria is proposed (Table 6.2)

6.5 Time Course of Clinical Aspects in Infancy

AE begins in the first months of life, usually around 3 months, but may be noted as soon as the first weeks of life and some mothers indicate that the skin of their infant is abnormal from birth. The lesions are usually symmetrical on limb extensor aspects and facial convexities, strikingly sparing (as noted by previous generations of physicians and dermatologists) the median part of the face, especially the tip of the nose. On the trunk, eczema disappears on the site covered by diapers, leaving a well-demarcated limit (Fig. 6.3), strongly suggesting a protective local effect on disease expression [2, 5] A flexural involvement can be seen early in infants, and the neck fold is commonly involved in the 1st year of life. At this stage, scalp involvement may indeed look seborrheic, with yellow squames and crusts, and cutaneous xerosis is not constant.

In the 2nd year of life, skin xerosis tends to become a more dominant feature. The type of lesions is highly variable depending on disease severity at the time of examination (flare-up or remission). However, in a given patient, the pattern distribution of eczematous lesions is fairly constant with "bastion" areas, especially on the hands and face. Acute oozing lesions lead to crusting and frequent impetiginization. They are usually not well limited. On the contrary, intermittently oozing and crusted recalcitrant lesions may appear to be well limited, taking on a nummular shape (nummular eczema in infancy is usually associated with other typical aspects of atopic eczema) (Fig. 6.4). On rare

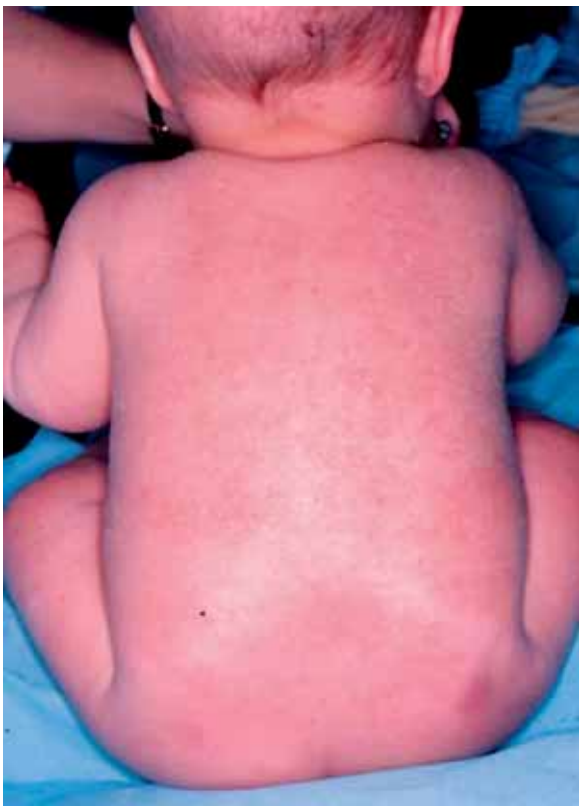


Fig. 6.3. The diaper area is not involved in the majority of infantile cases of atopic eczema

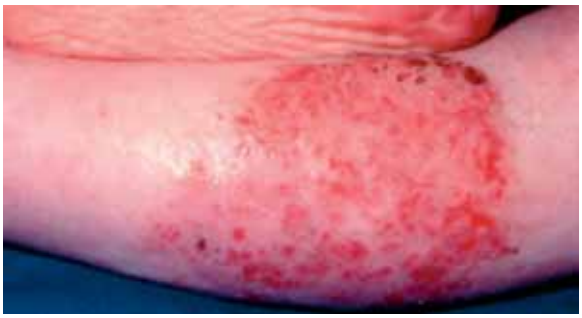


Fig. 6.4. Nummular eczema in a 18-month-old child with atopic eczema

occasions, atopic eczema in infancy may show figurate eruptions, with circinate borders and central healing. In minor forms, inflammatory lesions are not conspicuous and palpation can only mark the limits of abnormally rough skin.

Useful descriptive items to obtain an intensity score of AE in infancy include erythema, edema (edematous papules), excoriations (an objective marker of pruritus), oozing or crusting in relation with the acuteness of vesicular flare-ups [48]. Pruritus is usually demonstrable in the first months of life, causing sleep disturbance. True scratching by hand is preceded in the 2nd month of life by equivalent movements such as rubbing the cheeks against the bed sheets or the mother's clothes, and bed agitation with limb and trunk rubbing movements. As noted earlier, lichenification appears later in the 2nd year of life but seems to have an earlier onset in Black or Asian infants.

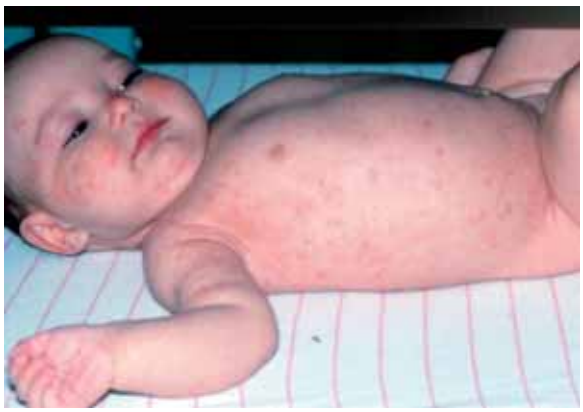


Fig. 6.5. Scabies is an important differential diagnosis and is frequently treated with topical corticosteroids first because of an erroneous diagnosis of eczema

6.6 Differential Diagnosis

A list of common and uncommon differential diagnoses for infants is listed in Table 6.3, which should be considered with the type and country of clinical practice in mind. In the vast majority of cases, the diagnosis of AE in infancy is straightforward and differential diagnosis is merely an academic exercise. However, in a busy practice, the high frequency of AE cases may blur the clinical acumen and it is not rare in a hospital setting to rectify a diagnosis of eczema that was hurriedly made (e.g., scabies, Fig. 6.5).

Thus, in all infants presenting with eczema, a history needs to be obtained, and they must be examined thoroughly, including growth assessment, mucous membrane inspection, lymph node and abdominal palpation, and pulmonary auscultation. In cases seen at the onset of symptoms, the major criterion of chronicity and relapsing course is lacking and the interpretation must remain cautious. In difficult cases, a biopsy should be taken when there is clinical uncertainty, especially to rule out a case of Langerhans-cell histiocytosis (Fig. 6.6), a rare disease but one that still suffers

Table 6.3. Differential diagnosis of infantile atopic eczema

Conditions considered	Major differential points
Scabies, acropustulosis of infancy	Palmoplantar involvement, axillary nodules (scabies), familial pruritus (scabies)
Infantile seborrheic dermatitis	Bipolar rash, pruritus rare or moderate, involvement of major folds
Psoriasis	Diaper area, scalp, face affected commonly in infants, pruritus mild or absent
Langerhans cell histiocytosis	Papular and sometimes purpuric rash, pruritus mild or absent, biopsy
Miliaria rubra	Transient, heat-induced, pruritus mild or absent
Papular urticaria (prurigo simplex)	Commonly affects limbs, uncommon in infancy, arthropod-borne
Gianotti-Crosti syndrome	May include papulovesicular lesions on limbs and face, sometimes pruriginous; anicteric hepatitis, lymph node enlargement, virus-induced (EBV in most cases)
Keratosis pilaris	No pruritus, stable, palpation of lesions
Frictional lichenoid eruption of childhood	Elbows, dorsum of hands, seasonal variation, pruritus variable [31]
Eosinophilic pustulosis of infancy	Starts mostly on scalp with recurrent crops of pustules; associated hypereosinophilia [40]
Asymmetric periflexural exanthem of childhood (APEC)	May last up to 4 months; early asymmetric stage of eruption useful to make a diagnosis [9]

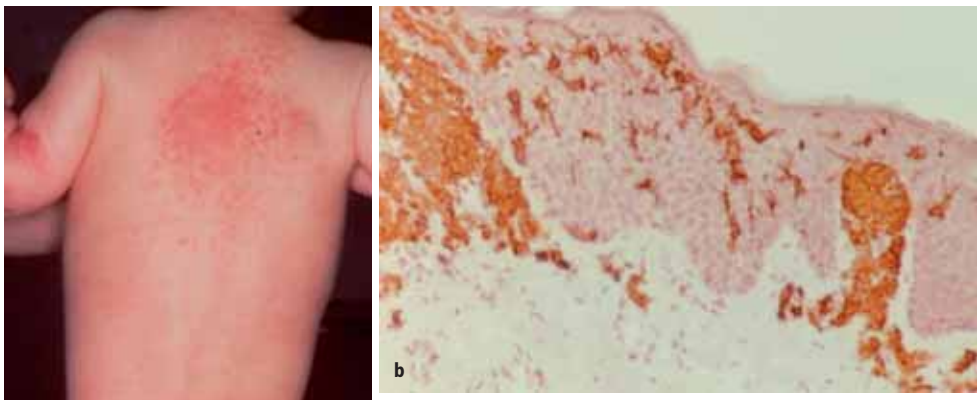


Fig. 6.6. a A cutaneous biopsy is useful to rule out Langerhans cell histiocytosis, a rare disorder commonly diagnosed as "eczema" at onset (**b** S 100 staining)

from delays in diagnosis, although it is easy to obtain specific cutaneous histopathology.

If there are other abnormal findings, such as cutaneous or often repeated infections, growth failure, purpura, unexplained fever, specific investigations must be implemented to diagnose an inheritable underlying trait, in which dermatitis may reveal a monogenic disorder affecting mostly the immune system or the skin barrier (Table 6.4 and Figs. 6.7 – 6.9).

Table 6.4. Heritable disorders associated with atopic eczema (translated and adapted from [47])

Involving mostly the epidermis or adnexa
AD ichthyosis vulgaris: difficult to diagnose early; examination of parents; early xerosis
X-linked recessive or autosomal dominant hypohidrotic ectodermal dysplasia, Christ Siemens Touraine: EDA/EDAR/XEDAR/NEMO genes with common impairment of TNF/TNFr-NFκb signaling during cutaneous development
Involving the immune system
XLR Wiskott Aldrich syndrome: purpura and thrombocytopenia (WASp gene dysfunction in T lymphocytes and platelets)
Selective IgA deficiency
AR severe combined immunodeficiency (SCID)
Hyper IgE syndrome (Job-Buckley), sporadic: skin and scalp abscesses, deep infections, coarse facies
Mixed or of uncertain status
AR Comel-Netherton syndrome (SPINK 5 gene encoding antiprotease LEKTI in epithelia and thymus)
AR Dubowitz syndrome: growth and mental retardation, dysmorphic facial syndrome

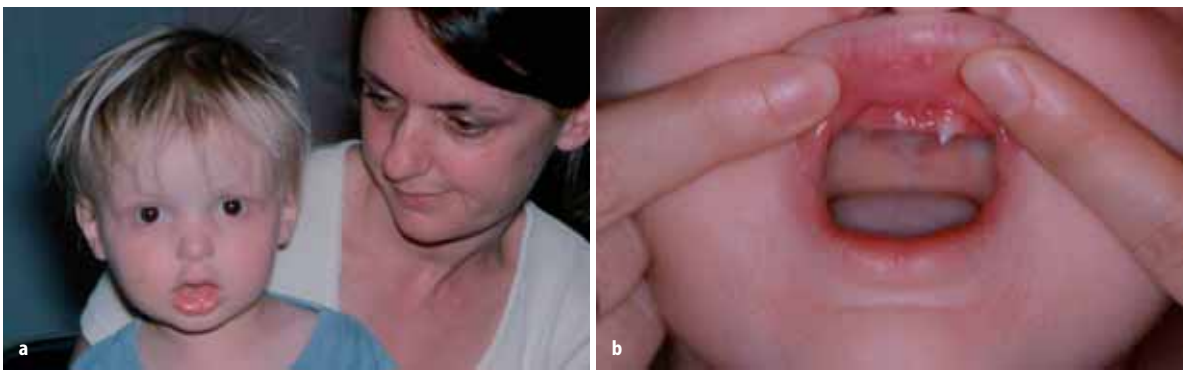


Fig. 6.7. a An 18-month-old child referred for suspected food allergy associated with moderate atopic dermatitis. The facies and delayed tooth eruption with (**b**) conic incisor are typical of X-linked hypohidrotic ectodermal dysplasia (mother found to be carrier with mild involvement)

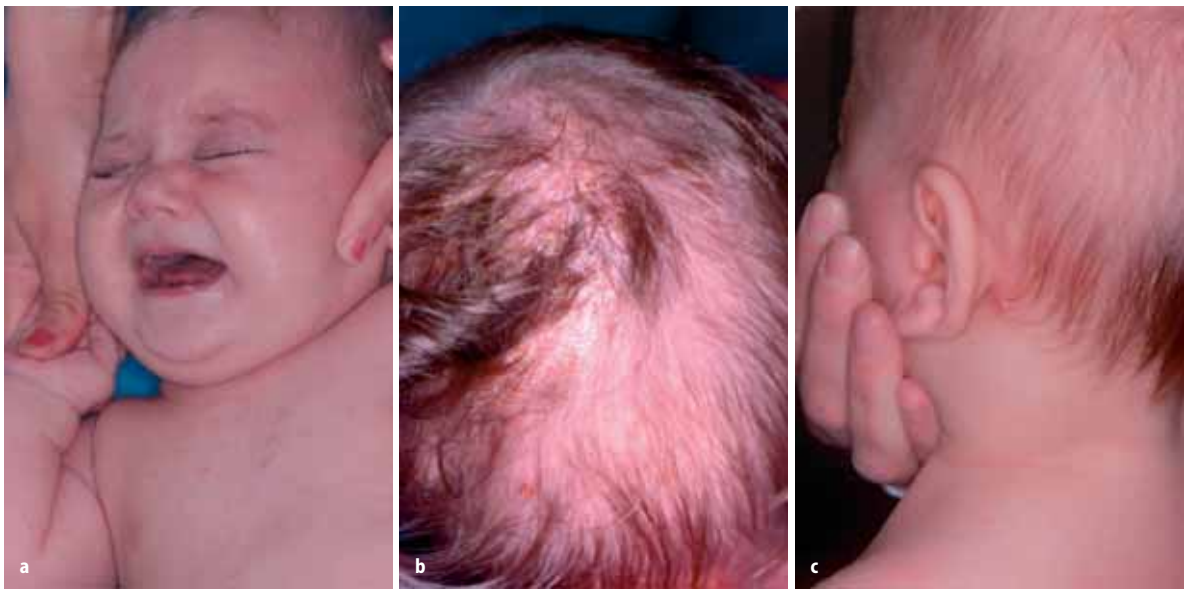
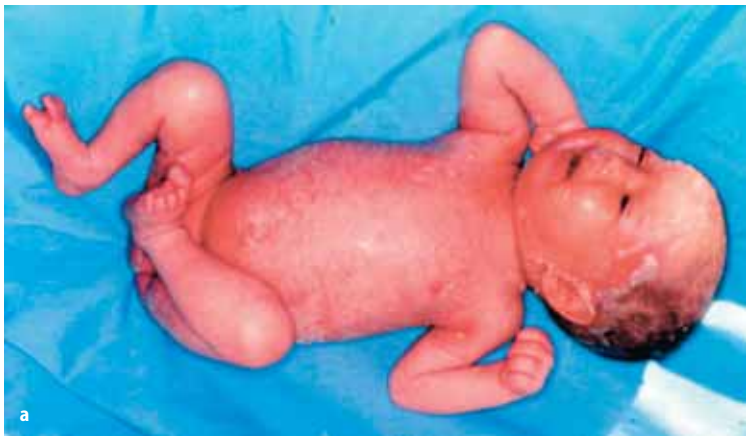


Fig. 6.8. a, b Hyper IgE syndrome. Typical facies with recurring scalp abscesses and suppurative lesions. Other sites with mild eczematous lesions. Initially needs to be distinguished from eosinophilic pustulosis of the scalp (**c**)



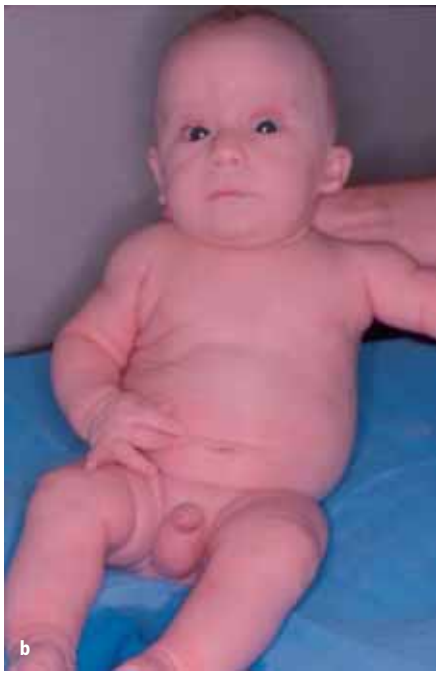


Fig. 6.9a, b. Netherton syndrome. **a** An erythrodermic form in infancy that evolved into a more localized form in childhood; **b** mild form of the disease in infancy that can be readily misdiagnosed as atopic dermatitis. Hair fragility and microscopic examination of hairs is helpful, and more recently skin biopsy to detect LEKTI protein as well as genetic testing

6.7 Complications

Superinfections by *Staphylococcus aureus* and *Herpes simplex* virus are the most common.

S. aureus colonizes atopic dermatitis skin, as shown by qualitative and quantitative bacteriologic studies on involved and noninflammatory skin. The limits between acute weeping lesions and clinical impetigo are not easy to determine (Fig. 6.10). Bullae suggest a diagnosis of bacterial superinfection and prompt a systemic treatment with antibiotics to avoid severe internal infections, especially osteomyelitis and bullous staphylococcal pneumonia. Subcutaneous bacterial complications are seldom encountered in infants.

Herpes is the most feared superinfection because of the severest forms (Fig. 6.11) known since Kaposi when the same clinical features were caused by vaccine inoculation to prevent smallpox. The recent preventive measures against bioterrorism have resuscitated the fear of smallpox and the use of topical calcineurin inhibitors has been questioned as a risk factor. A rapid change in the aspect of lesions and the presence of vesicles or smallpox-like pustules is an emergency in an infant that calls for the prescription of an appropriate antiviral treatment, on clinical grounds best confirmed by rapid diagnostic tests (polymerase chain reaction). Varicella is usually not more severe in infants with atopic eczema.

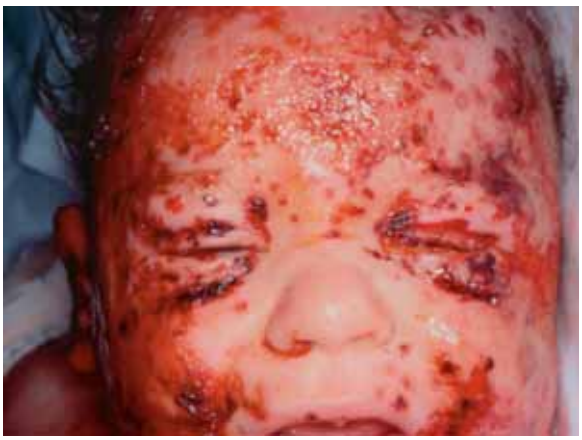
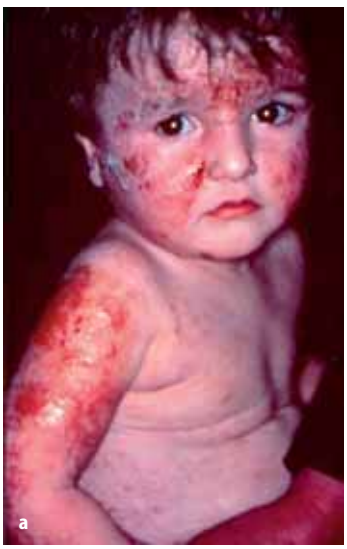


Fig. 6.11. Severe eczema herpeticum (Kaposi-Juliusberg syndrome) in an infant due to HSV1. Note the punched out lesions with pustules reminiscent of smallpox.

The proneness to both types of superinfection has been recently related to an insufficient local production of antimicrobial peptides [30].

Growth failure is usually associated with severe atopic eczema and sleeplessness is attributable to nocturnal pruritus. The monitoring of growth and development is mandatory as part of clinical evaluation of infants with atopic eczema. Other causes must be ruled out, such as intrauterine growth retardation, growth hormone deficiency, celiac disease, cystic fibrosis, etc. False-positive sweat tests have already been reported in the latter setting. When infantile eczema is properly treated, growth and development resume a normal pattern. The role of topical steroids is frequently put forward but exceptionally may cause growth retardation.



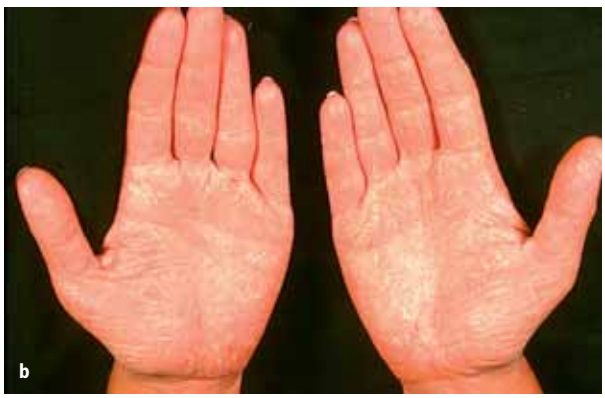


Fig. 6.10. Acute flare-up of atopic eczema associated with impetiginization

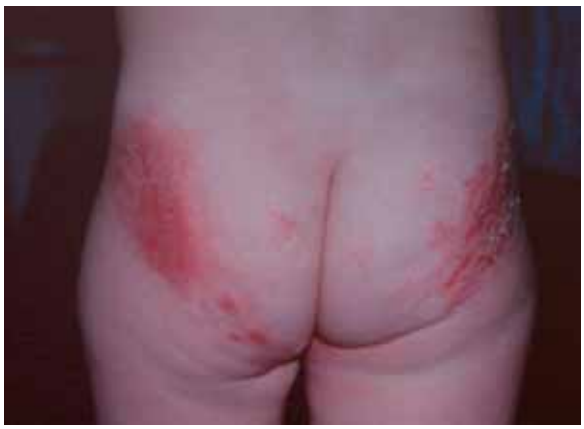


Fig. 6.12. Lucky Luke contact dermatitis to constituents of diapers

Contact dermatitis should be investigated when the response to conventional treatment is poor or when unusual sites are involved. The so-called Lucky Luke diaper dermatitis is a good example in infants (Fig. 6.12) [33].

6.8 Management

6.8.1 Prevention

Primary prevention is a major goal given the burden of disease and possible later respiratory involvement. In utero sensitization to allergens is difficult to manage, and at-risk babies have been submitted to various interventions without clear success until now, at best delaying the onset of symptoms. Substitutes to mother's milk such as highly hydrolysed casein or amino acids have been tested in controlled studies in high-risk infants and may decrease the severity of symptoms without affecting sensitization profiles [16, 44]. Delaying the introduction of solid foods until 6 months is generally advocated by pediatricians with a high interest in allergy because it has been shown that early solid feeding increases eczema and food allergy incidence [23]. Cow's milk and egg avoidance in the first 4 months in mothers decreases atopic eczema, but most physicians are reluctant to implement such measures which need a dietitian's supervision. Probiotics, especially lactobacillus BB, given to at-risk newborns, have been shown to decrease by half the incidence of atopic eczema at age 2, without decreasing allergen sensitization, possibly due to regulatory cytokine stimulation in the intestine (TGF-βΔand IL-10) [24]. Gamma linolenic supplementation in high-risk infants has also been tested and found beneficial [42]. The presence of furred pets in the baby's environment is a matter of debate, since recent studies do not indicate an increased risk or rather a protective factor, but the definition of at-risk groups in the studies may need improvement.

Secondary prevention is important when the diagnosis of atopic dermatitis is established. However, limited validated data exist, suggesting a better short- and long-term outcome following interventions, concerning both the course of eczema and that of asthma/rhinitis.

Diet and Secondary Prevention. Many studies have promoted the use of milk protein hydrolysates or even amino acid solutions to prevent food allergy when the infant could not be breast-fed or as a general preventive measure in high-risk infants. Such derivatives are costly and do not taste good. Soya milks do not come out better in comparison. The composition in essential fatty acids from vegetal origin of alternatives to maternal milk have raised concerns about both their potential role in increasing cutaneous inflammation but also in preventing brain development. Thus breast-feeding remains the most widely acknowledged preventive measure in the atopic infant, in spite of a host of data that are difficult to interpret or contradictory. Its demonstrated preventive action against infection is a good argument to maintain it both in developed and less developed countries. Its role in prevention of respiratory manifestations of atopy also continues to be debated.

Aeroallergens and Secondary Prevention. Food sensitization precedes aeroallergen sensitization, but the latter lasts longer and the incriminated allergens are clearly associated with asthma and allergic rhinitis attacks. The early detection of egg sensitization is a marker of later risk of asthma. Indoor allergens are important because children spend nearly 90% of their time indoors in Westernized countries. Indoor allergens such as house dust mite (HDM) allergens are a target for asthma prevention, but their contribution to the infant's eczema as contact allergens is probably underestimated. Patch testing infants is frequently positive with both

indoor and outdoor aeroallergens before the detection of specific IgE, suggesting a true penetration syndrome contemporaneous with atopic eczema onset, possibly due to a more permissive cutaneous barrier [38]. Polyurethane mattresses and pillows as well as house dust mite proof bedding can be advocated in high-risk infants, but this intervention has not been validated formally in infancy. The strategy used by asthmologists to reduce house dust mite concentrations under 2 mg/g of dust could be implemented and ideally checked by simple tests at home (the guanine test, ELISA).

6.9 Education and Compliance

Parents need to adhere to a therapeutic project delineated in common with the physician. A specialized and dedicated management of infants with atopic eczema is often lacking, and the parents are frequently discouraged by previous unskilled counseling and contradictory views given on their child's situation. Living with an infant with eczema may be a troublesome experience, due to lack of sleep in both infant and parents, as well as various worrisome effects on everyday life (diet, time for treatment, stigmatization, etc.). The child's personality may be affected as well.

Informing the family on the disease and its course, followed by an explanation on how to implement local treatments or better by a practical demonstration of skin care by a nurse on the child, can help in not overdramatizing the situation. Explanations must be clear and specific on the various aspects of care, and key points have to be repeated. Brochures and videos may help but cannot replace the time shared with the doctor and/or nurse. A priority for planning care is to assess previous treatments, especially amounts of topical steroids used and how they were used. A structured questionnaire is useful to obtain the history and to check the patient's aggravating factors one by one. The major points of the information given to the family are the following:

1. Atopic eczema is a chronic condition. Its treatment must also be chronic. This point must be clarified and repeated during the planning of therapy, whose aim is to improve the cutaneous status of the child significantly, which can be measured by a validated scoring system such as the SCORAD index. The perspective of a cure can be discussed but is not the major objective.
2. Topical treatment is mandatory. Local care can restore the cutaneous barrier compromised by the dermatitis. Inhaled steroids for asthma could be used as an example to persuade the family that local care is the equivalent for skin in a long-term treatment plan.
3. Topical corticosteroids are effective and do no harm when used properly under medical supervision. They do not trigger asthma. Their inadequate use is the major cause of both a feeling of helplessness and rejection of local therapies in some families. Physicians have their share of responsibility in this suboptimal use of active treatments. The new therapeutic class of calcineurin inhibitors (including tacrolimus and pimecrolimus) is not yet sufficiently evaluated to be considered as a mandatory alternative to topical corticosteroids, except in case of marked cutaneous atrophy, a rare finding in infants.
4. Alternatives to topical treatments associated with the environment and if necessary diet control are limited. They should be carefully weighed against conventional approaches based on previous compliance to a basic skin therapy regimen. Systemic treatments, besides antibiotics and antiviral drugs that may be occasionally needed, are given as adjuvants during flare-ups or in case of failure of an adequately administered topical treatment. This last item (failure of an adequately administered topical treatment) is of utmost importance for deciding on allergy testing, which is best envisaged as a part of therapy or management based on medically sound arguments, leading to environmental or diet changes. In severe forms, hospital admission remains justified to complete education and perform allergy or other tests adequately.
5. Information about aggravating factors must be given. Explanations and counseling need to be adapted to the family so that they fully understand, in a relaxed, nontense atmosphere, where the family's complaints should be taken seriously. A 45-min visit is commonly required initially. However, even a long visit, brochures and video are frequently not enough. A follow-up visit checking compliance to educational principles, with the help of a specialist nurse, is particularly useful. Psychological support, encouragement by the staff, examples from others

(in the case of an eczema school or following encounters in a specialized department), and of course clinical improvement motivate the family to pursue the efforts. In case of management success, the family becomes autonomous and responsible, which is the best sign of a successful technology transfer.

6.10 Practical Implementation of Treatment

A systematic review of atopic eczema treatments has been made by Hoare et al. [20]. Few treatments are evidence-based, and this review is a mandatory reading for those interested in this subject. The following section is not based on evidence but on personal experience and involvement in clinical research.

6.10.1 Decreasing Inflammation and Pruritus

Decreasing inflammation and pruritus is the major aim to help the patient rapidly.

6.10.1.1 Topical Treatment

In most cases, topical treatments can effectively treat atopic eczema flare-ups. The skin must be cleansed thoroughly to get rid of crusts and eliminate mechanical bacterial contaminants. Cleansers with or without antiseptics (the duration of action of antiseptics is very limited, thus mechanical cleansing is probably more important) can be used, in nonirritant and low-allergenic formulas available in various galenic forms (soaps, syndets, aqueous solutions). In infants, this first stage of gentle cleansing of the skin is easier directly on the changing table rather than directly in the bath. A further cleansing followed by a rapid rinse is done in the bath (33 – 34 °C, not more than 5 min). The short duration of the bath is designed to avoid epidermal dehydration. Topical products are easy to apply to the skin, still lightly moist, gently dried by padding with a towel, avoiding energetic friction.

Topical antibiotics (e.g., sodium fusidate cream or ointment) used twice daily improve lesional score in acute flare-ups and are useful mostly in short 2- to 4-day courses. Chronic use should be discouraged because of induction of bacterial resistance. A topical corticosteroid can be introduced after 2 – 3 days, in the potent or moderately potent range, once daily until clearance or frank improvement (4 – 8 days in routine practice). Tubular gauzes are most helpful to dress the young patient (after application of treatment) for the first days in severe cases requiring inpatient care (Fig. 6.13). TubiFast gauzes impregnated with topical corticosteroids have been mostly advocated by UK dermatologists, but their use is rather cumbersome and they have not been evaluated against standard care as outlined above [37].

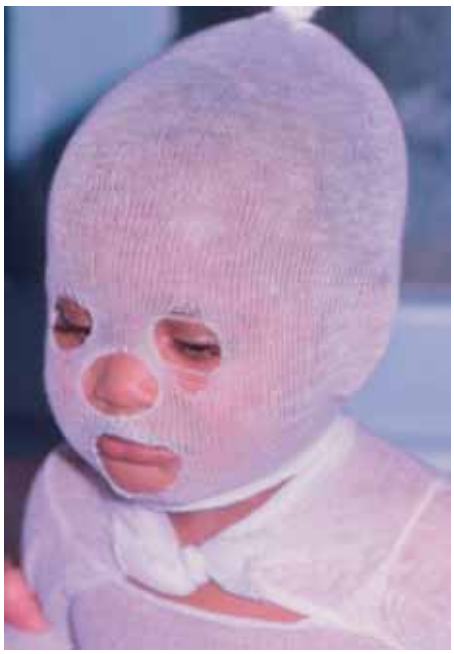


Fig. 6.13. Tubular dressing for acute flare-ups of atopic dermatitis

Maintenance treatment includes intermittent use of topical corticosteroids on inflammatory skin as needed (pruritus, sleeplessness, new flare-up). Generally, a small amount of topical corticosteroids two or three times a week (monthly amounts in the mean range of 15 g), associated with a liberal use of emollients (monthly amounts in the range of 300 – 400 g), provide good maintenance with SCORAD values below 15 – 20. Such monthly amounts of even potent topical steroids in children below 2 years of age do not have adverse systemic or local effects. The need to use different potency of topical corticosteroids according to the site

treated or to the phase of treatment (induction or maintenance) is not currently a matter of consensus among experts.

The recent introduction of macrolactam immunomodulators such as tacrolimus and pimecrolimus may change the strategy used for local treatments. Unlike tacrolimus, pimecrolimus has been tested in clinical trials in infants [19, 25] as a first-line treatment following emollients, topical corticosteroids being used as a rescue treatment. The cost-effectiveness of this approach as well as safety assessment await further studies.

6.10.1.2 Systemic Treatment

There is a very limited access to systemic drug treatment in infants with AE. Oral antihistamines (anti-H1) are of questionable interest for long-term treatment of infantile AE [10], but may be helpful to decrease pruritus and permit sleep during flare-ups. In this setting, sedative anti-H1 molecules such as hydroxyzine are frequently considered as more helpful than recent less sedative drugs.

6.10.2 Improving the Cutaneous Barrier

Predisposing barrier anomalies are suspected in AE, which may lead to easier early allergen introduction through the skin and more proneness to irritation and subsequent cutaneous inflammation. A lack of important stratum corneum intercellular lipids or an inadequate ratio between compounds (cholesterol, essential fatty acids, ceramides) would enhance transepidermal water loss, leading to epidermal microfissuring, which may also cause direct nerve ending exposure. A better molecular and biochemical knowledge of this predisposing background should give access to barrier-improving topical medications that can be used in infancy. Promising studies have recently been done in this area [7]. The cost of high-quality allergy-safe emollients generally refrains their use because such products are considered as nonprescription drugs, and the quantities needed are usually high (150–300 g per week). Their direct use on inflamed skin is poorly tolerated, and it is better to treat the acute flare-up first, as outlined above. Nonaggressive cleansing using syndets in milky form, unrinsed emulsions, or micellar solutions, as well as bath oils may also help to reduce the flare-ups.

6.10.3 Controlling and Preventing Aggravating Factors and Counseling

This time-consuming task is particularly important. Much time is needed to answer parents' questions. The major concern is to allow the child and family to have a life close to normal, avoiding unnecessary measures and putting too many constraints when avoidable. Thus the severity may guide the choices of the adviser. In a high-risk family with both parents involved with either skin or respiratory atopic disease, maximal pre-

Table 6.5. List of aggravating factors and hygiene counseling for infants

- Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and excessively warm clothing to avoid excessive sweating. New, nonirritating clothing designed for AE children currently evaluated.
- Tobacco: avoid exposure.
- Cool temperature in bedroom and avoid too many bed covers.
- Increase emollient use in cold weather.
- Avoid exposure to herpes sores. Urgent visit if flare-up of unusual aspect.
- Vaccines: normal schedule in noninvolved skin, including egg-allergic patients.
- Food allergens
  - Maintain breast-feeding until 6 months if possible and delay introduction of solid foods until 7th month or more (1 year) for egg, peanut, fish, exotic fruits. Avoid foods possibly containing peanut (marked "vegetable fat")
  - Otherwise normal diet, unless an allergy workup has proven the need to exclude a specific food.
- Indoor aeroallergens
  - House dust mites (routine)
    Adequate ventilation home; keep the rooms well aerated even in winter.
    Avoid wall-to-wall carpeting.
    Remove dust with a wet sponge
    Vacuum with an adequately filtered vacuum cleaner once a week all floors and upholstery.
    Avoid soft toys in bed (cradle), except washable ones.
    Wash bed sheets at a temperature higher than 55°C every 10 days.
  - House dust mites (high risk).
    Bed and pillow encasings in allergen-proof fabric.
  - Furred pets: advise to avoid preventively. If allergy demonstrated, be firm on avoidance measures.
- Pollens: close windows during peak pollen season in warm and dry weather and restrict stays outdoors if possible; aeration at night and early in the morning or in rainy weather; avoid exposure to at-risk situations (lawn mowing); use pollen filters in car; clothes and pets can vectorize aeroallergens, including pollens.

ventive measures must be advised. Early detection of asthma in infants with AE is also part of global management. Immunization, including those against measles in hen's egg allergy are safe [22], the only restriction being the quality of skin care to avoid superinfection at injection sites (Table 6.5).

6.10.4 Identification and Avoidance of Allergens

6.10.4.1 Background

The allergic part of atopic dermatitis continues to be debated and some authors still doubt its relevance relative to cutaneous symptoms, raising the question of the real need for allergy testing. Randomized controlled studies of avoidance interventions are lacking, or when these measures are taken (e.g., mattress encasings for house dust mite avoidance), they provide conflicting results. Thus, most opinions are derived from observational studies. Given the prevalence of the disease, the cost effectiveness of allergy investigations and allergen avoidance measures must be taken into account, but also few data are currently available. A preventive and probabilistic approach as outlined in Sect. 6.3 concerning the most common foods and aeroallergens is tenable in minor or moderate forms of AE, but severe forms resisting conventional treatments need a comprehensive allergy workup. As summarized in Table 6.6, allergy investigations have to be integrated into a global, graded management program. In severe forms of infantile eczema, highly restricted diets blindly prescribed rarely work in isolation, and may be dangerous. Tests must be done in conditions allowing a straightforward interpretation. Specific IgE testing may be the only possible initial diagnostic approach in infants with generalized eczema. Prick and patch testing give more comprehensive and relevant information. Patch testing needs a near-clearance of lesions beforehand, thus necessitating intensive dermatological treatment allowing a remission of symptoms. Specialized management is thus highly recommended, and severe cases may even need to be hospitalized so that tests can be done in good conditions. The help of a dietitian is also needed to implement and assess avoidance diets in infants.

Table 6.6. Graded approach situating allergy testing within general management of infantile atopic eczema

- **Minor forms** SCORAD < 15: emollients, counseling (including diet)
- **Moderate forms:** SCORAD 15 – 40: id + topical steroids ± macrolactam derivatives ± antiH1 and antibiotics during flare-ups; allergy workup if more than 30 g/month topical steroids
- **Severe forms:** SCORAD > 40, id + compliance assessment, hospitalization if needed, consider other treatments if no response to dermatological treatments and allergen avoidance

Food Allergens. About one-third of infants with AE have immediate reactions to at least one major allergen in single- or double-blinded challenges [36]. These patients have mostly persistent, moderate to severe AE. The relevance to skin symptoms has been studied by Niggemann et al. [29], who carried out immediate and late evaluations in a group of hospitalized patients challenged with foods, showing that out of 77 positive challenges, 50 % resulted in immediate reactions, 27 % in late reactions, and 23 % in combined immediate/late reactions. The majority of early reactions are urticarial rashes, some associated with gastrointestinal symptoms or wheezing. Late reactions consist in eczema worsening, and are better predicted by epicutaneous patch testing of foods [21]. The usual diagnostic approach is to perform skin prick tests with commercial extracts or fresh foods after careful history taking, and, if positive, to propose single- or double-blind placebo-controlled food challenges after at least a 3-week period of avoidance of incriminated foods. Those challenges need inpatient supervision. A clear history of immediate reaction is sufficient to bypass this procedure. In clinical practice, it is not possible to make clear conclusions concerning late reactions, and most data concerning food allergy in infants with AD are derived from immediate reactions. The benefit of avoidance diets following positive food challenges is variable, suggesting that if foods aggravate eczema, they represent only a fraction of the expression of the disease. It is noteworthy that food allergy symptoms may persist after eczema has cleared up, but that the reverse also holds true (tolerance to foods with persisting eczema). Simpler techniques need to be implemented to diagnose true food allergy, such as labial food challenges [32], which can be used on an outpatient basis.

Contact Allergens. A poor or incomplete response to treatment or the need to increase amounts of topical

steroids and the involvement of areas usually not involved in AE (e.g., the buttocks, see Fig. 6.12) should prompt contact allergy testing, after removal of suspected contact allergens. When formal contact allergen testing is not possible, an open test using repeated application of the offending product can be done. The interpretation of patch tests in infants is sometimes difficult, and irritant reactions are especially common with metals. A restricted battery usable in infants and children has been proposed, because of lack of space to test all products and the possible risk of sensitizing patients [33].

Aeroallergens. Patch test positivity to pollens, house dust mites, and less frequently animal dander is surprisingly high in infants (averaging 80 % in infants less that 1 year of age), with the known difficulty of separating out nonspecific irritant reactions from true contact allergy. However, clear HDM-positive reactions encourage both parents and physicians to apply avoidance measures carefully.

6.11 Prognosis of Infantile Eczema

Since Brocq's views on the subject in 1903 (Table 6.1), we have not made much progress. Vicker's study [43] was considered as a landmark in the 1980s, because of the personal follow-up of a large cohort until adolescence. The reverse pattern, later age at onset, and female sex had an overall poor prognosis. When reviewed recently [15, 39], these views were found contradictory with more recent studies, and globally the subject of natural history and risk factors was considered as requiring more work from good cohort studies. In 60 % of infants, their eczema will probably clear up for good; severe infantile cases are probably more prone to being long-lasting, and asthma will develop in around 40 % of infants with atopic eczema with at least one first-degree relative with atopic disease – either atopic dermatitis, asthma, or allergic rhinitis (ETAC study).

6.12 Conclusions

Since early scientific studies such as Hall's one century ago, reviewed at the beginning of this chapter, infantile eczema is frequently envisaged as a model to understand atopic eczema. It is intriguing that no real breakthrough in pathophysiology has been made despite one century of investigations. Positions are still entrenched between those in favor of food allergy considering skin involvement as the target of an allergic mechanism (inside-out view), and those in favor of a primary skin disease leading to local/systemic immune disturbances associated with allergic manifestations (outside-in view). Infantile eczema is difficult to understand within the static intrinsic/extrinsic paradigm, because studies show a progression of sensitizations associated with duration of disease. The importance of the skin as a gateway of entry for persisting aeroallergen sensitization is probably a major feature that has been neglected for too long. The allergen penetration syndrome view of infantile eczema [38] is a unifying concept between skin and later respiratory disease that may allow preventive intervention.

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