Chapter 1
Clinical Guide Introduction

Quote by A. Fischer *[1]:*

"I have indicated that in the search for causative agents of contact dermatitis the physician must literally suspect everything 'under the sun' (and the sun, itself), including those agents to which the patient has been exposed for years without prior difficulty. The patient's total environment with its flora and fauna, topical medications, clothing, cosmetics and other contactants encountered in work or play may have to be investigated. The victim must then be armed with knowledge that will enable him to distinguish friend from foe and to avoid his personal villains no matter how disguised. Thus, the victim, the patient, will be enabled to enjoy his environment with safety."

Introduction

Contact dermatitis (CD) is one of the leading reasons for patients to seek dermatology consultation, with an estimated 72 million people in the United States afflicted with this condition. There are two main types of CD, all of which result from contact of the skin or mucous membranes with an exogenous agent. The most common form of CD,

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accounting for ~80 % of cases, is irritant contact dermatitis (ICD), followed by allergic contact dermatitis (ACD), which represents ~20 % of cases and is the primary focus of this handbook [2–4]. Recent patch test studies in US-based populations, confirmed equal prevalence of contact allergy in pediatric and adult populations [5]. Furthermore, rates of contact allergy vary based on regional and social differences in allergen exposure, as well as differing referral patterns, selection criteria for patch testing, and allergens tested [6]. Finally, much less commonly observed are contact urticaria (CU) and protein contact dermatitis, which are beyond the scope of this handbook, but are mentioned briefly for completeness, and the reader is directed to key sources on these topics below.

Background on Diagnostic Patch Testing in the US

In the United States, Marion Baldur Sulzberger first introduced the epicutaneous patch test technique, developed by Josef Jadassohn, in the 1930's at New York Skin and Cancer Unit.

Furthermore, in 1931 Helene Ollendorff-Curth, also trained by Jadassohn, came to the United States and introduced patch testing to industries in order to improve safety measures on commercially available products. Over the next three decades, patch testing clinics were developed worldwide, and in 1962, the Scandinavian Committee for Standardization of Routine Patch Testing began to formalize patch testing procedure and materials. By the early 1980s, the Food and Drug Administration (FDA) proposed a ban on the production and sale of allergens for the patch tests based on the lack of availability of scientific evidence for its procedure, safety, and efficacy. A mandate was set for companies to standardize their medicinal chemicals.

In response, the North American Contact Dermatitis Group (NACDG) developed a research arm and worked with Stiefel Laboratories to help the German subsidiary of

Hermal receive approval for the European based Hermal/Trolab 20 standard allergen test. This test was available through the American Academy of Dermatology (AAD). Then, under the leadership of Howard Maibach and the Pharmacia-Upjohn Company, the 20 Allergen Test was transformed into what is now the commercially available Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test™ (Mekos Laboratories A/S, Hillerod, Denmark), whose first 23 allergens were approved by the FDA in 1997 [7]. By 2012, 12 new allergens/mixes had received FDA approval for commercial availability for a total of 35 chemicals/mixes.

Approximately 1,700 new synthetic chemicals on average are being brought to the U.S. market annually and, notably, the Environmental Protection Agency (EPA) tests only chemicals that demonstrate evidence of significant health risk potential. Thus, the situation is such that only about 25 % (of the 82,000 chemicals in use in the U.S.) have ever been subject to basic testing, which is why A. Fischer is astute in his observation that the physician should suspect anything and everything under the sun.

Fortunately, major culprit allergens have been identified through extensive tracking by the International Contact Dermatitis Research Group (ICDRG) and the North American Contact Dermatitis Group (NACDG) over the last 30 years. This has allowed for the compilation and generation of series of panels of allergens, which can serve as a base point to initiate screening. For example, available series include: the American Contact Dermatitis Society (ACDS) 80 Core Series [8], the fragrances series [9], the vehicle and cosmetic series [10], and then occupationally customized panels such as dentistry [11] and bakery panels [12] (see Tables 1.1, 1.2, 1.3, 1.4, and 1.5). Further series be can found on Chemotechnique Diagnostics' (Sweden) website, http://www.chemotechnique.se/Online-Catalogue.htm, or the allergEAZE™ (Calgary, AB) website, http://www.allergeaze.com/allergens.aspx?ID=Series.

As many of these allergens are found in a variety of household and cosmetic products, as well as items with which patients come in contact with daily, tailoring the patch test to patients'

Table 1.1 American contact dermatitis society (ACDS) 80 core series

Substance	Handbook #
1. Nickel sulfate 2.5 % pet.[a]	72
2. Myroxylon pereirae 25 % pet.[a]	4
3. Fragrance mix I 8 % pet.[a, c]	42
4. Quaternium 15.2 % pet.[a]	35
5. Neomycin 20 % pet.[a]	71
6. Budesonide 0.1 % pet.[a]	24
7. Formaldehyde 1 % aq.[a, c]	34
8. Cobalt chloride 1 % pet.[a, c]	13
9. p-tert-Butylphenol formaldehyde resin 1 % pet.[a]	74
10. P-Phenylenediamine 1 % pet.[a]	73
11. Potassium dichromate 0.25 % pet.[a, c]	76
12. Carba mix 3 % pet.[a, c]	80
13. Thiuram mix 1 % pet.[a]	81
14. Diazolidinyl urea 1 % pet.[a]	36
15. Paraben mix 12 % pet.[a]	75
16. Black rubber mix 0.6 % pet.[a]	7
17. Imidazolidinyl urea 2 % pet.[a]	38
18. Mercapto mix 1 % pet.[a]	83
19. Methylchlorisothiazolinone/ Methylisothiazolinone 100 ppm. aq.[a]	68
20. Tixocortol-21- pivalate 1 % pet.[a]	23
21. Mercaptobenzothiazole 1 % pet.[a]	82
22. Colophony 20 % pet.[a]	18
23. Epoxy resin 1 % pet.[a]	30
24. Ethylenediamine 1 % pet.[a]	32
25. Wool alcohol 30 % pet.[a]	67

Table 1.1 (continued)

Substance	Handbook #
26. Benzocaine 5 % pet.[b]	8
27. Bacitracin 20 % pet.[a]	3
28. Mixed dialkyl thioureas 1 % pet.	84
29. Fragrance mix II 14 % pet.	51
30. Benzophenone-3.3 % pet.	6
31. Disperse blue 106.1 % pet.[a]	27
32. Disperse blue 124.1 % pet.	28
33. Gold sodium thiosulfate 0.5 % pet.[a, c]	65
34. Ethyl acrylate 0.1 % pet.	1
35. Compositae mix 6 % pet.	20
36. Sesquiterpene lactone mix 0.1 % pet.	21
37. DMDM hydantoin 1 % pet.	36
38. Tosylamide formaldehyde resin 10 % pet.	88
39. Methyl methacrylate 2 % pet.	2
40. Cinnamic aldehyde 1 % pet.	44
41. Propylene glycol 30 % aq.	77
42. Cetyl steryl alcohol 20 % pet.	N/A
43. 2-Bromo-2-nitropropane-1,3-diol (Bronopol) 0.5 % pet.[a]	39
44. Sorbitan sesquioleate 20 % pet.	85
45. Cocamidopropylbetaine 1 % aq.[c]	14
46. Glyceryl thioglycolate 1 % pet.	N/A
47. Ethyleneurea melamine-formaldehyde 5 % pet.	N/A
48. Iodopropynyl butylcarbamate 0.1 % pet.[c]	66
49. Chloroxylenol (PCMX) 1 % pet.	N/A
50. Glutaraldehyde 1 % pet.	N/A
51. Ethyl cyanoacrylate 10 % pet.	N/A

(continued)

TABLE 1.1 (continued)

Substance	Handbook #
52. Benzyl alcohol 10 %	See #4
53. Benzalkonium chloride 0.1 % aq.[c]	5
54. Methyldibromoglutaronitrile 0.5 % pet.	69
55. Propolis 10 % pet.[c]	N/A
56. n,n-Diphenylguanidine 1 % pet.	N/A
57. Lanolin alcohol (Amerchol 101) 50 % pet.	67
58. Triethanolamine 2 % pet.[c]	N/A
59. Amidoamine 0.1 % aq.	15
60. Desoximethasone 1 % pet.	See #'s 23–25
61. Triamcinolone 1 % pet.	See #'s 23–25
62. Clobetasol-17- propionate 1 % pet.	See #'s 23–25
63. Hydrocortisone-17-butyrate 1 % pet.[a]	25
64. 4-Chloro-3-cresol (PCMC) 1 % pet.	N/A
65. Benzophenone-4 2 % pet.	N/A
66. Chlorhexidine digluconate 0.5 % aq.	N/A
67. Ylang ylang 2 % pet.	N/A
68. Phenoxyethanol 1 % pet.	N/A
69. Sorbic acid 2 % pet.	N/A
70. 2, 6-Ditert-butyl-4-cresol (BHT) 2 % pet.	N/A
71. Disperse Orange 3.1 % pet.	N/A
72. 3-(Dimethylamino)propylamine (DMAPA) 1 % aq.	N/A
73. Oleamidopropyl dimethylamine 0.1 % aq.[c]	N/A
74. Dl Alpha Tocopherol 100 %	29
75. Cocamide DEA 0.5 % pet.	N/A

Table 1.1 (continued)

Substance	Handbook #
76. Lidocaine 15 % pet.	11
77. Dibucaine 2.5 % pet.	10
78. Jasmine absolute 2 % pet.	N/A
79. Tea tree oil 5 % pet.	N/A
80. Triclosan 2 % pet.	N/A

[a]TRUE Test allergen
[b]Caine mix (containing benzocaine) is a TRUE Test allergen
[c]Interpret reactions with caution, mild irritant and/or low clinical relevancy

Table 1.2 Fragrance series (perfumes/flavors)

Substance	%	Vehicle
4-(4-hydroxy-4-methyl pentyl)- 5 petrolatum 3-cyclohexene-1-carboxaldehyde (Lyral)	5	Petrolatum
Amylcinnamic alcohol	1	Petrolatum
Amylcinnamic aldeyhde	1	Petrolatum
Anisyl alcohol	1	Petrolatum
Bay leaf oil	2	Petrolatum
Benzaldehyde	5	Petrolatum
Benzyl alcohol	1	Petrolatum
Benzyl salicylate	1	Petrolatum
Benzylbenzoate	1	Petrolatum
Cinnamic alcohol	1	Petrolatum
Cinnamic aldehyde	1	Petrolatum
Citral	2	Petrolatum
Citronellal	2	Petrolatum
Citronellol	1	Petrolatum
Coumarin	5	Petrolatum

(continued)

TABLE 1.2 (continued)

Substance	%	Vehicle
d-limonene	2	Petrolatum
d-limonene	3	Petrolatum
Eugenol	1	Petrolatum
Farnesol	5	Petrolatum
Fragrance mix [A]	8	Petrolatum
Fragrance mix [B]	8	Petrolatum
Geraniol	1	Petrolatum
Hexyl cinnamic aldehyde	10	Petrolatum
Hydroxycitronellal	1	Petrolatum
Isoeugenol	1	Petrolatum
Jasminum officinale oil (jasminum grandiflorum)	2	Petrolatum
Majantol	5	Petrolatum
Oak moss absolute	1	Petrolatum
Oil cedar	10	Petrolatum
Oil neroli	2	Petrolatum
Oil of bergamot	2	Petrolatum
Oil of cinnamon	0.5	Petrolatum
Oil of cloves	2	Petrolatum
Oil of eucalyptus	2	Petrolatum
Oil of lemon	2	Petrolatum
Oil of lemon grass	2	Petrolatum
Oil of rose	0.5	Petrolatum
Oil of rosemary	0.5	Petrolatum
Orange oil	2	Petrolatum
Phenyl salicylate	1	Petrolatum
Salicylaldehyde	2	Petrolatum
Vanillin	10	Petrolatum

Table 1.3 Cosmetic series

Substance	%	Vehicle
1,3,5-tris(2-hydroxyethyl)-hexahydrotriazine (Grotan BK)	1	Petrolatum
2,5-diazolidinyl urea (Germall® II)	1	Petrolatum
2-bromo-2-nitropropane-1,3-diol (Bronopol)	0.5	Petrolatum
2-hydroxy-4-methoxy-benzophenone	10	Petrolatum
4-chloro-3,5-xylenol (PCMX)	1	Petrolatum
4-chloro-3-cresol (PCMC)	1	Petrolatum
Abietic acid	10	Petrolatum
Abitol	10	Petrolatum
Amerchol L101	50	Petrolatum
Benzophenone 4	10	Petrolatum
Benzyl alcohol	1	Petrolatum
Benzyl salicylate	1	Petrolatum
Butylhydroxyanisole (BHA)	2	Petrolatum
Butylhydroxytoluene (BHT)	2	Petrolatum
Cetylstearylalcohol	20	Petrolatum
Chlorhexidine digluconate	0.5	Water
Chloroacetamide	0.2	Petrolatum
Clioquinol	5	Petrolatum
Cocamidopropyl betaine	1	Water
Coconut diethanolamide (cocamide DEA)	0.5	Petrolatum
Cold cream	100	
Diethanolamine	2	Petrolatum
Dimethylaminopropylamine		Petrolatum
Diphenylthiourea	1	Petrolatum
DMDM hydantoin	1	Petrolatum
Dodecyl gallate	0.2	Petrolatum

(continued)

Table 1.3 (continued)

Substance	%	Vehicle
Ethylenediamine dihydrochloride	1	Petrolatum
Hexamethylenetetramine	1	Petrolatum
Imidazolidinyl urea (Germall® 115)	2	Petrolatum
Iodopropynyl butylcarbamate	0.2	Petrolatum
Isopropylmyristate	10	Petrolatum
Methylchloroisothiazinolone/ methyliisothiazinolone – Kathon CG	0.01	Water
Methyldibromo glutaronitrile (MDBGN)		Petrolatum
Methyldibromo glutaronitrile/ phenoxyethanol (MDBGN/PE)-Euxyl K 400	1	Petrolatum
Octyl gallate	0.2	Petrolatum
Paraben mix [B]	12	Petrolatum
Petrolatum	100	Petrolatum
Phenoxyethanol	1	Petrolatum
Phenyl salicylate	1	Petrolatum
Phenylmercuric acetate	0.05	Petrolatum
Polyethylene glycol ointment	100	
Polyethylene glycol-400	100	
Primin	0.01	Petrolatum
Propyl gallate	0.5	Petrolatum
Propylene glycol	20	Water
Quaternium 15 (Dowicil 200)	1	Petrolatum
Sesquiterpenelactone mix (2 ml)	0.1	Petrolatum
Sodium benzoate	5	Petrolatum
Sodium disulphite	1	Petrolatum
Sodium-2-pyridinethiol-1-oxide (Sodium-Omadine)	0.1	Water
Sorbic acid	2	Petrolatum

Table 1.3 (continued)

Substance	%	Vehicle
Sorbitan monooleate (Span 80)	5	Petrolatum
Sorbitan sesquioleate	20	Petrolatum
Stearyl alcohol	30	Petrolatum
Tea tree oil, oxidized	5	Petrolatum
Tert-butylhydroquinone	1	Petrolatum
Thimerosal	1	Petrolatum
Tolu balsam	20	Petrolatum
Tosylamide/formaldehyde resin	10	Petrolatum
Triclosan	2	Petrolatum
Trithanolaminee	2.5	Petrolatum
Tween 40	10	Petrolatum
Tween 80	10	Petrolatum
Vanillin	10	Petrolatum
Wool alcohols ointment	100	
Wool fat	30	Petrolatum

Table 1.4 The dentistry series (dental materials)

Substance	%	Vehicle
(2-hydroxyethyl)-methacrylate	1	Petrolatum
1,3-butandiol-dimethacrylate	2	Petrolatum
2-hydroxy-ethylacrylate	0.1	Petrolatum
2-hydroxypropyl-methacrylate	2	Petrolatum
Amalgam (Ag 13.9 %, Cu 2.4 %, Sn 3.5 %, Zn 0.02 %)	20	Petrolatum
Amalgam (Hg 2.5 %, Ag 1.7 %, Cu 0.3 %, Sn 0.4 %, Zn 0.025 %)	5	Petrolatum
Ammoniated mercury	1	Petrolatum
Ammonium tetrachloroplatinate	0.25	Petrolatum

(continued)

Table 1.4 (continued)

Substance	%	Vehicle
Benzoyl peroxide	1	Petrolatum
BIS-GMA	2	Petrolatum
Bisphenol A	1	Petrolatum
Bisphenol-A-dimethacrylate	2	Petrolatum
Copper sulphate	1	Water
Diurethane-dimethacrylate	2	Petrolatum
Ethyleneglycol-dimethacrylate	2	Petrolatum
Eugenol	1	Petrolatum
Mentha piperita oil (peppermint oil)	2	Petrolatum
Methyl methacrylate	2	Petrolatum
N,N-dimethyl-p-toluidine	2	Petrolatum
Palladium chloride	1	Petrolatum
Potassium dicyanoaurate	0.002	Petrolatum
Sodium thiosulfoaurate (gold)	0.25	Petrolatum
Tetracaine-HCl	1	Petrolatum
Tin (II) chloride	0.5	Petrolatum
Triethyleneglycol-dimethacrylate	2	Petrolatum

Table 1.5 The bakery series

Substance	Conc. %	Vehicle	Conc. molality (m)
Vanillin	10.0	Petrolatum	0.657
Eugenol	2.0	Petrolatum	0.122
Isoeugenol	2.0	Petrolatum	0.122
Sodium benzoate	5.0	Petrolatum	0.347
BHT	2.0	Petrolatum	0.091
Menthol	2.0	Petrolatum	0.128

Table 1.5 (continued)

Substance	Conc. %	Vehicle	Conc. molality (m)
Cinnamyl alcohol	2.0	Petrolatum	0.149
Cinnamal	1.0	Petrolatum	0.151
2-tert-Butyl-4-methoxyphenol (BHA)	2.0	Petrolatum	0.111
Trans-Anethole	5.0	Petrolatum	0.337
Sorbic acid	2.0	Petrolatum	0.178
Benzoic acid	5.0	Petrolatum	0.409
Propionic acid	3.0	Petrolatum	0.405
Octyl gallate	0.25	Petrolatum	0.009
Dipentene (oxidized)	1.0	Petrolatum	0.073
Ammonium persulfate	2.5	Petrolatum	0.110
Benzoylperoxide	1.0	Petrolatum	0.041
Propyl gallate	1.0	Petrolatum	0.047
Dodecyl gallate	0.25	Petrolatum	0.007

specific exposure history can be very effective when used in conjunction with an appropriately broad- based screening panel. Customizing patch testing chambers allows for a comprehensive approach to testing by placing specific allergens or product samples into individual chambers on separate panels then applying the panels to unaffected regions of the patient's back.

Allergic Contact Dermatitis (the Disease State Once the Patient Has Developed Contact Allergy)

ACD is a complex immunologic reaction that ultimately results in a delayed (~48–120 h) presentation, referred to as a Type IV hypersensitivity reaction. This immune response is character-

ized by two main stages, sensitization and elicitation. An individual may become sensitized to a particular substance when his or her skin barrier is impaired, allowing for the entry of exogenous allergens into the epidermis. These allergens or haptens are small, lipophilic chemicals with low molecular weight (<10,000 Da) that bind with self proteins to form complete antigens upon entry into the epidermis. Dendritic cells, which are the antigen presenting cells (APCs) of the skin, then uptake and express these complete antigens on cell surface major histocompatibility complexes (MHC). The antigen is then presented by dendritic cells to naïve antigen-specific T-cells in the regional lymph nodes. These naïve T-cells then differentiate into effector/memory T-cells, which are capable of acting on APC's in the future [13–16].

Elicitation, the second phase of ACD, refers to the clinical dermatitic presentation, and occurs after repeated exposure to a particular allergen to which memory T-cells have been cloned. Exposure may occur transepidermally or systemically through ingestion, inhalation or intravenous entry [17]. In this stage, T-helper cells dominate as opposed to T-suppressor cells, which would create a state of relative or complete tolerance [16].

Because this process is delayed, patients may have difficulty discovering or temporally associating the initial source of their dermatitis, especially if it was years prior; therefore, patch test screening with an appropriate base panel is of utmost importance. Moreover, the distribution of the dermatitis may not follow the exposure pattern. ACD can present as a local, generalized, or ectopic dermatitis.

Adolescents [Age 13–17]

Childhood presentations of ACD are becoming more recognized as a significant problem, accounting for approximately 20 % of all cases of pediatric dermatitis [15, 16]. Moreover, adolescents account for a large proportion of pediatric ACD, especially in females when compared to their male counterparts, according to international literature. This trend has been observed with particular allergens, such as nickel and fragrance,

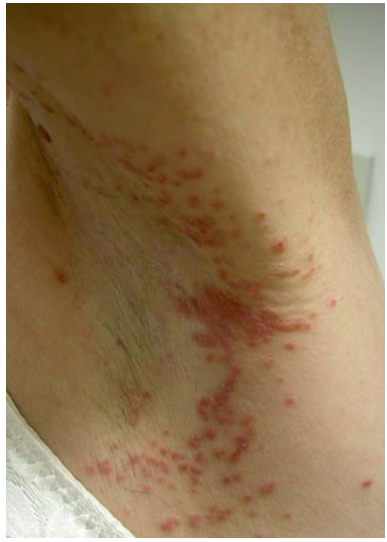

Figure 1.1 Sparing of axillary vault with allergic contact dermatitis

likely due to their presence in classically female sources, i.e. jewelry, cosmetics, and fragranced personal products [16, 18]. Recent studies, however, have reported an even distribution of allergens across all pediatric groups without noting gender bias [19, 20]. One relevant source of ACD in adolescents is sports equipment, i.e. wrist supports, shin and knee guards [21–23], athletic tape [24], and swimming goggles [25], often due to the allergen p-tert-butylphenol formaldehyde resin [26]. In addition, the warm, moist, occluded environment to which athlete's skin is subjected, may also make them more susceptible to ACD. The moisture may also contribute to chemical breakdown and release of allergens [27].

Clinical Presentation

ACD often presents with pruritic, eczematous papules and plaques, and occasional vesicles and bulla (Figs. 1.1, 1.2, 1.3, and 1.4). Because these descriptive terms are not unique to ACD, distinguishing it from AD and ICD can prove to be a challenge [16]. More specifically, acute ACD and AD often have similar morphological appearances, and furthermore,

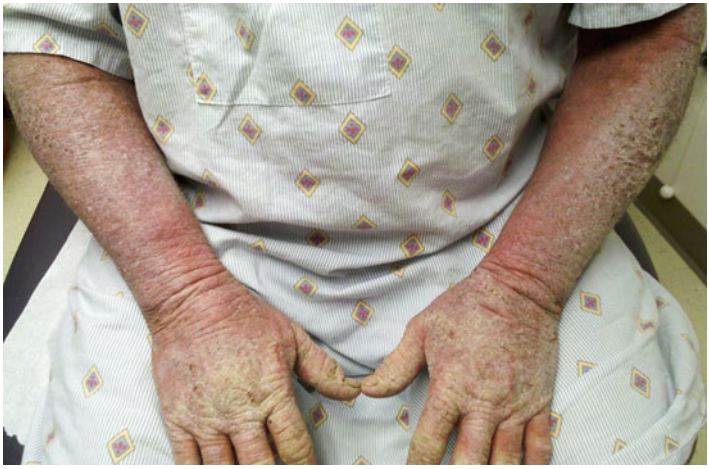

FIGURE 1.2 Erythroderma from advanced allergic contact dermatitis

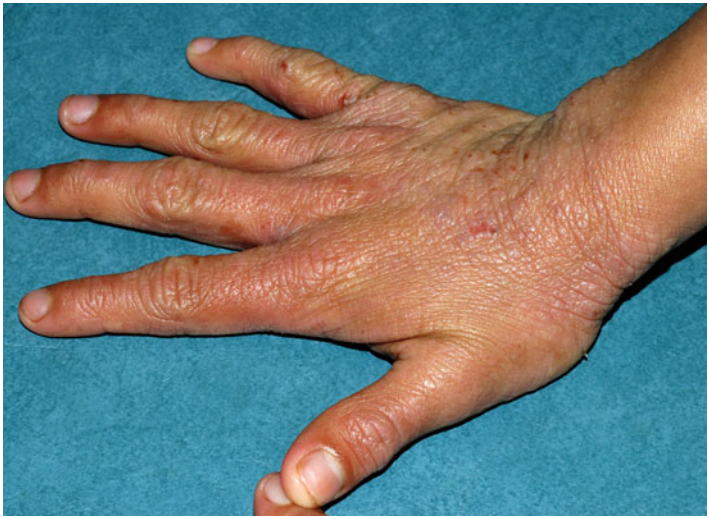

FIGURE 1.3 Allergic contact hand dermatitis

the two may occur simultaneously. In fact, it has been suggested that AD may predispose individuals to developing ACD due to a damaged epidermal barrier to allergens [28, 29]. Acute presentations of ACD and ICD may be distin-

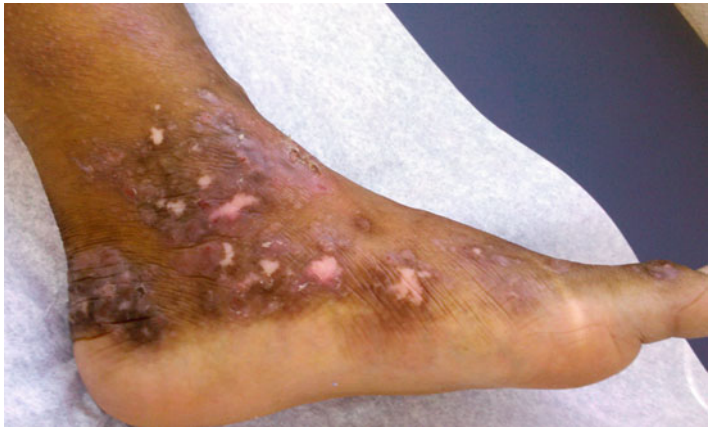

FIGURE 1.4 Chronic, allergic contact dermatitis of the foot, with lichenification and scarring

guished based on their temporal relationship to the inciting event as well as clinical distribution (see Table 1.6) [15, 16, 30]. ACD may present in an ectopic manner, meaning that the location of the dermatitis is not directly related to exposure site. This can occur in different ways, such as by transferring an allergen from one region of the body to another. For example, AD sites may flare after exposure to nail polish upon scratching [29] or eyelid dermatitis may ensue after a cashier rubs his or her eyes after handling monies. Even more challenging to diagnose are idiopathic (id) ACD reactions, which are non-specific, widespread eruptions that occur when the patient contacts a particular allergen [15, 16].

Irritant Contact Dermatitis

ICD is not considered an immunologic reaction, but rather is related to direct contact with an irritating substance that damages epidermal keratinocytes and induces inflammation, without activating an immune cascade. Therefore, previous chemical exposure and prior sensitization are not required for this reaction [31]. Classic examples of irritants include urine (diaper dermatitis), soap (hand dermatitis), and saliva

Table 1.6 Differences between acute ACD vs. acute ICD

Type of dermatitis	Temporal relationship to the inciting event	Clinical distribution	Symptoms
Allergic contact	Delayed hypersensitivity reaction	Induration or papulovesicular eruptions often expand beyond the location of contact	Usually pruritus
	Often presenting 48 h to up to 3 weeks	Ectopic patterns can be observed	
		Idiopathic (id) reactions are possible	
Irritant contact	Usually within 24 h	Appears as well-demarcated, erythematous, and sometimes follicular papules and plaques	Usually burning
	Concentration of the offending substance is inversely related to time of onset	Usually confined to areas of contact exposure	

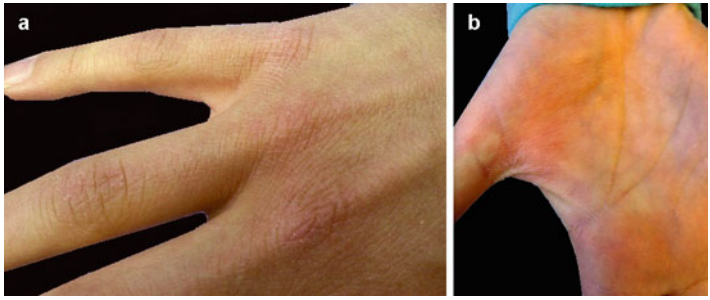

FIGURE 1.5 Irritant contact dermatitis of the dorsal (**a**) and palmar (**b**) surfaces of the hand

(lip licker dermatitis) (Fig. 1.5). Moreover, the severity of an ICD reaction is not solely dependent on the concentration of the instigating agent, but is directly proportional to the exposure time as well [15, 32].

Contact Urticaria

Unlike the type IV delayed immunologic reaction of ACD, CU is mediated by an immediate IgE type I immunologic reaction. Clinically, CU appears as a wheal and flare reaction, appearing within 30 min of exposure to a eliciting substance and resolving within hours [33]. Testing is usually performed by an allergist, who uses the RAST (radioallergosorbent test) or prick testing. Desensitization can then be attempted, which is much more difficult with Type IV reactions [16].

Protein Contact Dermatitis

The term protein contact dermatitis (PCD) was introduced in 1976 by Hjorth and Roed-Peterson [34], and refers to the development of a Type-I, immediate, IgE-mediated reaction upon exposure to protein. Clinically, the most common presentation of PCD is chronic or recurrent eczema; however,

urticaria may also be observed upon contact with particular proteins, such as certain foods and drinks (almonds, banana, carrot, celery, kiwi, melon, tomato, seafood, cow's milk), airborne ragweed particles, and natural rubber latex [33, 35].

Clinical Diagnosis

Investigative history and diagnostic clues are important elements to making a proper diagnosis of ACD. For instance, distinguishing between ACD and AD can be challenging, especially when occurring simultaneously. Luckily, certain clinical clues can increase the index of suspicion for ACD, such as new-onset, and/or a progressing or deteriorating dermatitis that is recalcitrant to standard therapies [36]. Epicutaneous patch testing, however, is the gold standard for the diagnosis of ACD [15, 16, 30] (see Table 1.7) [15, 28].

Table 1.7 Allergen determination for comprehensive patch testing

Patient history	**Clinical pattern of dermatitis**
Personal hygiene products Patient Close contacts (due to connubial dermatitis)	Local: dermatitis may relate to region of direct contact, i.e. peri-umbilical dermatitis linked to nickel allergy due to jean snaps and belts
Home environment	Ectopic: dermatitis may relate to region of indirect contact, i.e. peri-ocular dermatitis after rubbing eyes with nail polish
Medical history	Skin memory: dermatitis presents in region of previous exposure upon re-exposure to source at a different site, i.e. ingestion of chocolate (containing nickel) causes a peri-umbilical reaction
	Systemic, generalized: widespread appearance of dermatitis after systemic exposure, i.e. ingestion, intravenous, intramuscular, inhalation

Pre-patch Consult and Education

In the pre-patch education/instruction session, a provider must explain basic guidelines prior to testing (see Table 1.8) [36] as well as the testing procedure. As these instructions can be extensive, patients may not be willing or able to follow these rules. Therefore, a basic explanation of ACD being a delayed reaction in the initial consultation often helps patients to understand the lengthy testing timeline. There may be some patients, however, that do not appear capable of understanding all of the instructions and explanations, and the provider must then assess whether they would be a proper candidate as well [28]. Not only may the test itself be inaccurate based on patient's inability to follow instruction, but subsequent attempts at avoidance may not be possible.

Table 1.8 Patch testing guidelines

Guideline	Timeline
No creams or lotions on their back or pre-determined application site	Day of testing through final interpretation
No showering (cannot get application sites wet)	Application to final interpretation
No excessive sweating	Application to final interpretation
No topical steroids or topical calcineurin inhibitors on predetermined application site	1–2 weeks prior to application through final interpretation
No oral corticosteroids	Within 2 weeks prior to patch testing and through final interpretation
No IM corticosteroids	Within 4 weeks prior to patch testing and through final interpretation
No sun or UV light on the area to be tested	Weeks prior to testing through final interpretation
Oral antihistamines are allowed	Prior to and during testing

Pediatric Patch Testing

Pediatric patch testing poses more of a challenge when compared to testing adult patients. Selectivity of proper candidates not only includes taking a patient's age into account, but their family's ability to understand the process and their willingness to complete the journey. In addition, patch testing itself can be limited by the relatively smaller surface area available for chamber application (especially in dermatitic patients). Therefore, there is an increased need for selectivity when choosing which allergens to include in the series. Logistically, it is also difficult to ask a young child to sit still for a long period of time during patch application, removal, and interpretation. Moreover, patients' parents or legal guardians must be made aware that the procedure has not received Food and Drug Administration indication in pediatric patients [28]. Preliminary avoidance of allergens with a high likelihood of reactivity is especially helpful with pediatric patients, as testing may not be necessary if the patient has shown >50 % improvement in their condition in 4–6 weeks of avoidance. This also allows for a snapshot of the family's ability to comply with an avoidance plan.

Procedure Outline (see Fig. 1.6)

Patch testing can be achieved by using either commercially available pre-packaged allergen panels or by loading each allergen onto individual chambers on a tape strip. Some types of the patient's own products may also be applied directly to patch testing chambers, and placed on patients in addition to individual component chemicals [37] (Fig. 1.7). Panels of allergens and/or products should be placed on unaffected areas of patient's backs or arms in linear configurations and marked according to a pre-determined number scheme (Figs. 1.8 and 1.9). Securing these panels with hypoallergenic tape, such as hypafix tape ™ (Smith & Nephew, London, UK), is crucial, as these strips of allergens must remain in place under occlusion for 24–48 h. The 48 h point was selected to allow for optimized time of contact with the substance without increasing the

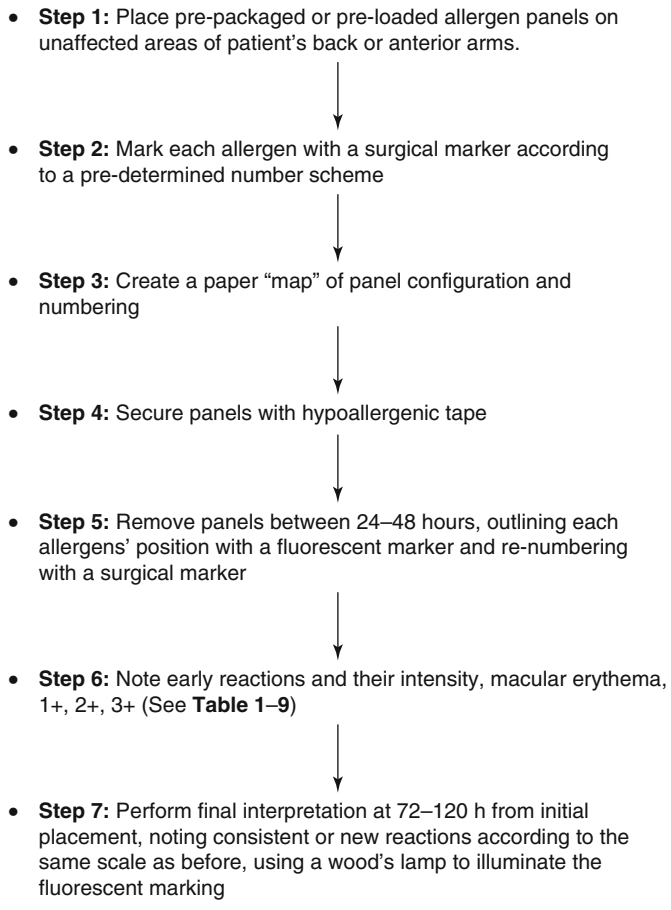

FIGURE 1.6 Patch testing algorithm

number of irritant reactions [38]. Of note, the German Contact Dermatitis Research Group (DKG) suggests a 24 h contact time for children ages 6–12.

An initial reading of the patch testing sites is performed upon removal of the allergen panels at the 48 h point and outlining individual chambers with a fluorescent marker (Fig. 1.10). Skin changes, such as erythema, induration, papules, vesicles, and blistering are noted at this time, and

FIGURE 1.7 Sample from an athletic shoe is removed using a punch biopsy instrument, dissected into parts, such as cloth and foam, and placed in patch testing chambers

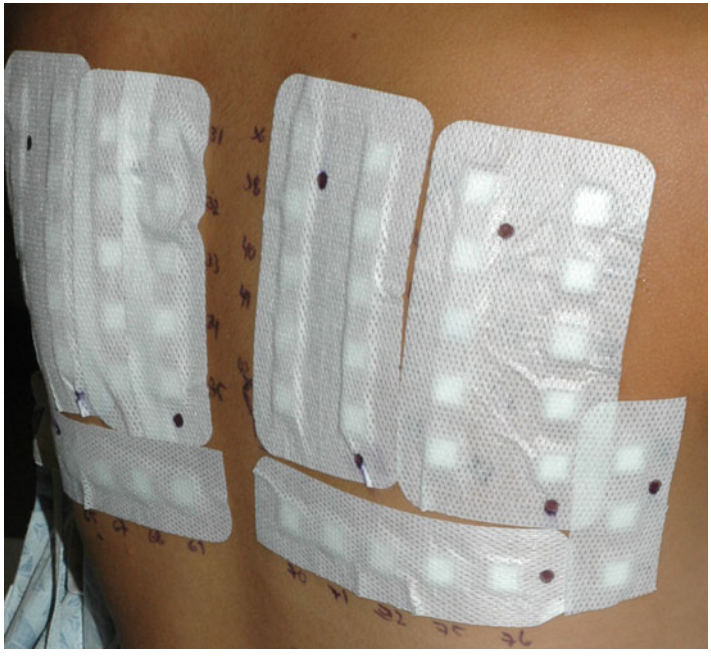

FIGURE 1.8 Patch test application. Panels of allergens placed in linear configurations and marked according to a pre-determined number scheme

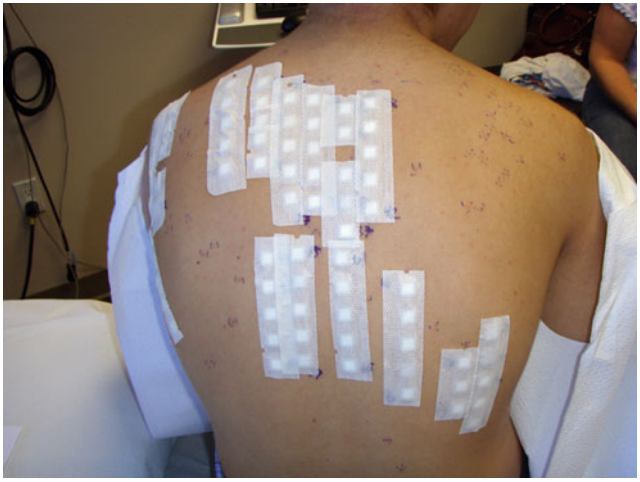

FIGURE 1.9 Avoidance of marked regions due to pre-existing dermatitis

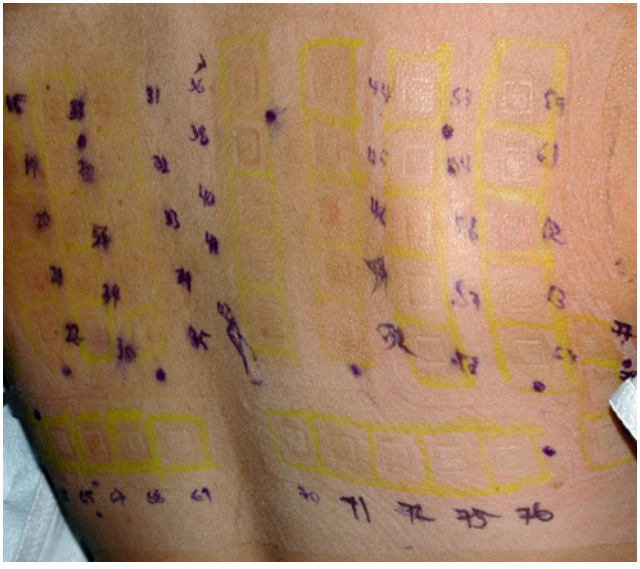

FIGURE 1.10 Patch test removal. An initial reading of the patch testing sites is performed at the 48 h point, with chambers outlined in highlighter and each allergen re-numbered with surgical marker

Table 1.9 Reaction rating scale

Macular erythema	Faint to pronounced erythema without elevation
1 +	Induration +/– erythema
2 +	Papules +/– induration and erythema
3 +	Vesicles and/or bulla +/– papules, induration and erythema

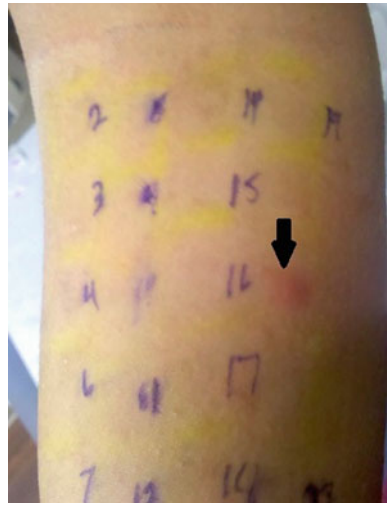

Figure 1.11 Final interpretation, macular erythematous reaction (*arrow*) to p-tert butylphenol formaldehyde resin (PTBFR)

rated accordingly. Reactions may range in intensity from macular erythema to a 3+ positive patch test (PPT) (see Table 1.9). However, the final interpretation must be done at a delayed reading in 72–120 h from initial placement, as initial cutaneous changes may be due to ICD, of which the majority resolve by the final interpretation (Figs. 1.11, 1.12, 1.13, and 1.14). In addition, 48 h may not be long enough for some of these type IV delayed reactions to appear or peak in intensity [15, 16]. Notably, corticosteroids, neomycin sulfate, and sodium gold thiosulfate appear late (see Table 1.10) [39, 40]. The final interpretation can be aided by the use of a wood's lamp, which will illuminate the highlighter in order to locate and directly feel the patch testing sites (Fig. 1.15).

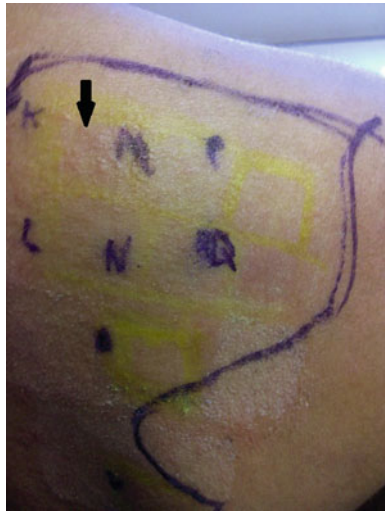

FIGURE 1.12 Final interpretation, 2+ reaction to bacitracin (*arrow*)

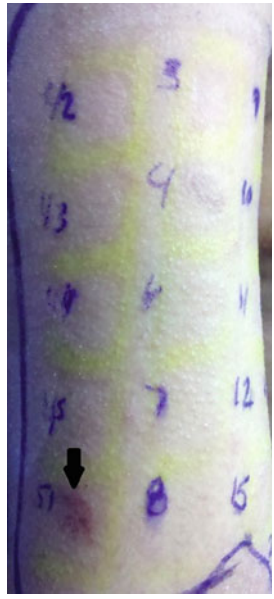

FIGURE 1.13 Final interpretation, 2+ reaction cobalt chloride

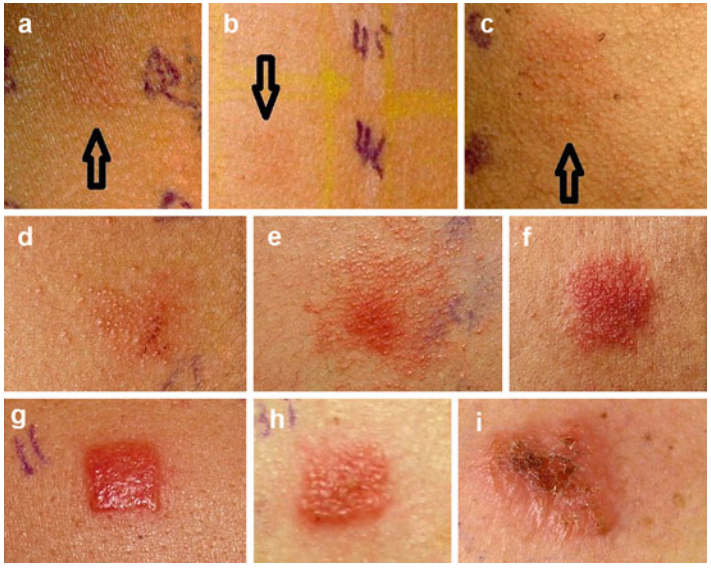

FIGURE 1.14 Reactions. (**a**) macular erythema; (**b**) macular erythema; (**c**) 1+ reaction; (**d**) 1+ reaction; (**e**) 2+ reaction; (**f**) 2+ reaction; (**g**) 2+ reaction; (**h**) 2+ reaction; (**i**) 3+ reaction

TABLE 1.10 Early vs. late reactions

Early reactions	**Late reactions**	**Crescendo reactions**
Balsam of Peru (*Myroxylon pereirae*)	Acrylates	Cocamidopropyl betaine
Carbamates	Compositae	
Thiuram	Corticosteroids (budesonide)	
	Formaldehyde releasing preservatives	
	Neomycin sulfate	
	Sodium gold thiosulfate	
	Textile dyes	

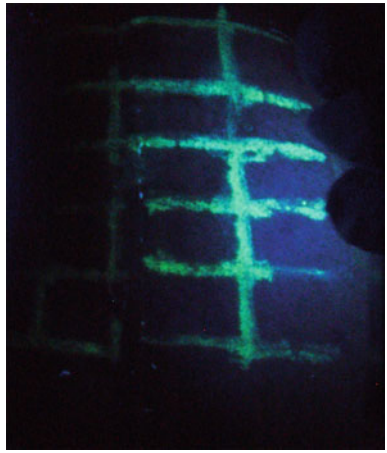

Figure 1.15 Final interpretation with the use of a wood's lamp to illuminate the highlighter in order to directly feel the patch testing sites

Certain chemicals and products, however, are not designed to be used under occlusion or to remain in contact with a patient's skin for long periods of time, and for that reason, a provider may decide to test particular products by employing provocative use testing. This form of testing, also called, repeat open application testing (R.O.A.T.) utilizes the inner or anterior arm of the patient, and involves placing a small amount of the product in question to a 2.5 cm drawn circle twice daily for 7 days (see Fig. 1.16). Importantly, this technique does not involve occluding chemicals as in classic patch testing; therefore, the allergen potency is not as great, which decreases risk of intense reactions, but also may require longer time to elicit a response.

Expected Adverse Reactions of Patch Testing

The most common adverse reactions associated with patch testing are expected cutaneous changes at the sites that were in contact with the testing substances, especially if the patient exhibited contact allergy (PPT). These reactions may include erythema, induration, papules, and vesicles, occasionally accompanied by pruritus, burning and inflammation at the site of application.

1. Place a small amount of each product in question into the corresponding drawn circle twice daily for 7 days.
2. For products that are intended to be 'washed off', rinse the product off 30–60 s after application, not worrying about products mixing together, as this is how they are used in daily routines.
3. If burning, erythema, or visible signs of irritation develop, discontinue use of the product and return to the clinic for visual inspection of the application site by a trained professional.

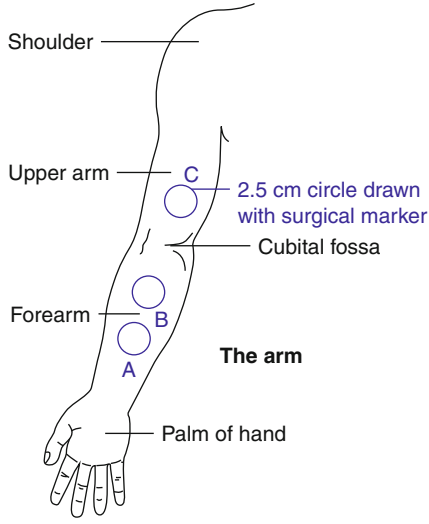

FIGURE 1.16 Repeat open application testing (R.O.A.T.)

Less commonly seen are pustular and blistering reactions, post-inflammatory hypo/hyper-pigmentation, and persistent granulomatous reactions. The most rare of reactions would be anaphylactic type reactions, which have been reported as individual case reports in which the patients have had contact urticarial syndrome (Type I) or developed a Type I hypersensitivity reaction to the agent. Some patients may experience a worsening of their initial dermatitis, which can serve as a diagnostic clue in assigning clinical relevance, as this phenomenon can be observed when one is tested and reacts to the same allergen that contributed to the initial and current presentation.

Moreover, based on information extrapolated from adult studies, active sensitization to one of the allergens tested at the standardized concentrations are very rarely reported (0.0–0.69 %) [40–43]. Published concentrations of chemicals used in commercially available patch testing kits are associated with the fewest side effects and are generally accepted [44]. Ultimately, the potential risks and side-effects presented

by patch testing are considerably outweighed by its usefulness, both as a diagnostic tool and as a guide to avoiding clinically relevant specific contact allergens.

Post-patch Education – Avoidance

While patch testing can provide a diagnosis of ACD and facilitate discovery of culprit allergens, it is patients that are responsible for the resolution of their dermatitis. This is because ***avoidance*** is crucial in the treatment of ACD, and can only be achieved with proper patient education. A post-patch testing session is necessary to inform the patient and their families of potential sources of exposure based on a thorough explanation of what their clinically relevant, positive allergens are and where they are often found. Patient-directed literature is available and should be provided to patients to aid in this endeavor. As there are endless products commercially available, teaching patients how to read the ingredient labels is also important, but there are online databases available for this purpose as well. Individualized lists of "safer" alternatives can then be generated, by entering relevant, positive allergens into the database [28]. Both programs also offer information about various allergens. There are two main programs that can provide this service, the Contact Allergen Management Program (C.A.M.P.) and the Contact Allergen Replacement Database (C.A.R.D.) [45, 46]. Products on these listings should be used with caution, however, as patients are generally not patch tested for every chemical ingredient. For this reason, educating the patient and family on performing provocative use testing or R.O.A.T. should be performed.

Management and Therapy (see Fig. 1.17)

Avoidance of causative allergens is the most crucial component of ACD resolution and management [47]. As mentioned earlier, patch testing can provide a means of discovering

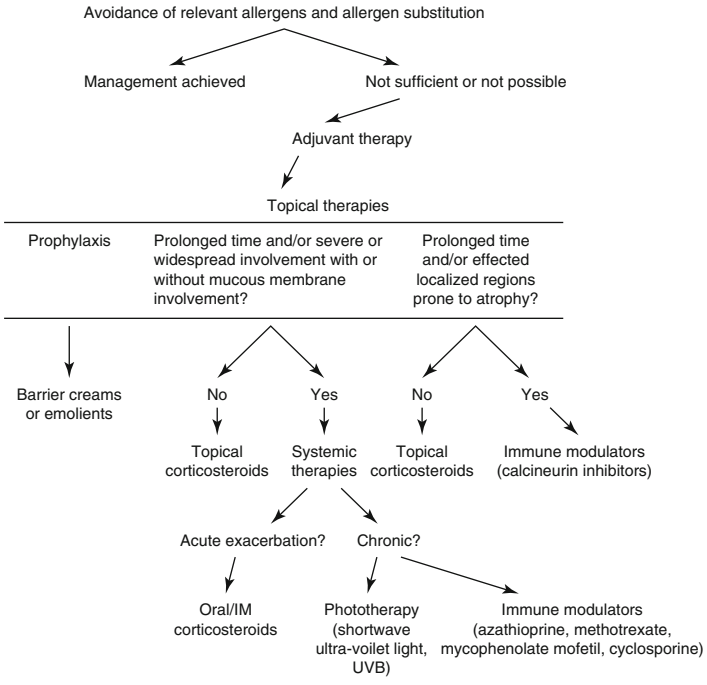

FIGURE 1.17 Management algorithm

relevant, positive allergens, allowing a provider to focus post-patch education on how to avoid specific chemicals [28, 47]. Patients are also educated on allergen substitution, which is aided by certain resources, such as the Alternatives for the 2007 NACDG Standard Screening Tray [48] and a 4-part series providing data from the American Contact Alternatives Group [49–52]. This series focuses on facial cosmetics, hair products, lip and dental care products, as well as personal care products. With these interventions, it may be possible to achieve a sustained remission.

There are times, however, when complete avoidance is not possible or when avoidance is not sufficient to clear a dermatitis outbreak. Moreover, patch testing may fail to identify

any or all inciting agents, especially if multiple chemicals are involved. Adjuvant measures, such as topical and/or systemic therapies may be necessary in these instances. In addition, physical barrier creams or emollients, such as petrolatum, can be utilized in many different situations as a form of exposure avoidance or prophylaxis. Topical agents are used as first line therapy, specifically corticosteroids, which may elicit side effects or induce sensitization to the vehicle ingredients or corticosteroids themselves with prolonged or widespread use [53–55]. Due to the issues surrounding long-term use of topical corticosteroids, topical immune modulators, such as calcineurin inhibitors [56, 57], may prove beneficial, especially in regions of thin skin or those prone to atrophy, such as the face and intertriginous areas. The next step in management involves the use of systemic therapies, which may be necessary for severe or widespread dermatitis with or without mucous membranes manifestations, or for dermatitis that continues to progress despite the use of topical agents.

Oral corticosteroids, such as prednisone [58], can be effective for acute exacerbations of ACD and tapered after symptoms are controlled. For chronic cases, however, 'steroid sparing' agents should be considered, such as phototherapy, usually with shortwave ultra-violet light (UVB), and systemic immune modulators (azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine) [47].