



Diagnosis and management of allergic contact dermatitis in children: common allergens that can be easily missed

Sharon E. Jacob^a, Nikoleta Brankov^b, and Alastair Kerr^c

Purpose of review

Contact dermatitis is an economically burdensome pediatric disease, and it is important to know the top allergens that have remained as top offenders for over the last decade.

Recent findings

A comparative analysis of the 20-allergen screen was done against the current top 40 pediatric allergens, and it revealed that the 20-allergen screening series would have theoretically only captured 47.5% of the relevant contact allergens (52.5% failure to detect rate). In addition, the T.R.U.E. Test (SmartPractice, Phoenix, Arizona, USA) would have revealed 60% of the top 40 allergens (40% failure to detect rate).

Summary

Patch testing in children has become a more common practice, and management requires the identification and avoidance of the offending allergen from the sensitized person's environment.

Keywords

allergic contact dermatitis, patch testing, preemptive avoidance strategy

INTRODUCTION

Contact dermatitis is a spectrum of conditions resulting from dermatologic reactivity to exogenous substances. There are two main subtypes, namely irritant and allergic. *Irritant* contact dermatitis (ICD) is an inflammatory reaction that requires no prior sensitization (specific antigen-primed immune response). *Allergic* contact dermatitis (ACD), on the other hand, is an acquired delayed hypersensitivity (Type IV) response, and accounts for 20% of contact dermatitis in children and occurs with the same frequency in children as adults. Proper management of contact dermatitis includes appropriate detection of allergens and implementation of accurate avoidance measures for those sensitized.

IRRITANT CONTACT DERMATITIS

The most common type of exogenous dermatitis in both children and adults is ICD, accounting for about 80% of cases. High offending irritants in childhood include biologic sources (e.g., saliva, urine and/or feces, caterpillars, and plants) and chemicals found in personal care and household cleaning products (e.g., surfactants and biocides). Surfactants may elude detection as a cause, if the exposure is chronic and the

reaction is low grade or flares a concomitant endogenous dermatitis (e.g., atopic dermatitis). ICD does not require sensitization and may occur with variation in individual susceptibility.

ALLERGIC CONTACT DERMATITIS

The manifestation of ACD represents a complex immune system response that includes sensitization and elicitation. Sensitization involves processing an allergen (hapten) by dendritic cells, presentation to the T cells in the regional lymph nodes, and clonal expansion of memory T cells, which can migrate back to the skin and elicit a reaction on subsequent exposure to the hapten. With elicitation, memory T cells are activated leading to cytokine IL-1, IL-6, and

^aDepartment of Dermatology, ^bDepartment of Medicine, Loma Linda University, Loma Linda, California, USA and ^cDepartment of Dermatology, Crosshouse Hospital, Kilmarnock, Scotland, UK

Correspondence to Sharon E. Jacob, MD, Professor of Dermatology, Department of Dermatology, Loma Linda University, 11370 Anderson Street, Suite 2600, Loma Linda, CA 92354, USA. Tel: +1 909 558 2890; fax: +1 909 558 2442; e-mail: sjacob@contactderm.net

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KEY POINTS

- Contact dermatitis is an economically burdensome pediatric disease.
- Current evidence suggests the sensitivity and specificity of patch testing is 70 and 80%, respectively.
- Twelve of the top 40 allergens can potentially remain elusive if only a basic screening patch test is performed.
- False negative reactions may occur if standard patch testing is utilized in the case where the allergen is a photo-activated chemical.
- The remission state for contact dermatitis is dependent on the ability to both detect and avoid.

granulocyte-macrophage colony-stimulating factor production, as well as mast cell and macrophage activation, with resultant inflammation and cellular destruction.

It should be considered in all patients with chronic recalcitrant dermatitis or those with worsening endogenous dermatitis. However, the threshold for testing in children remains high and many are unlikely to be patch tested, despite safety and efficacy studies indicating that patch testing is a valuable tool when used properly for confirmatory diagnosis.

DIAGNOSIS AND TESTING

In cases of ICD, diagnosis is often made by clinical presentation and history. Patients and providers alike are often able to make the temporal connection between the offending agent and the skin reaction, as a significant number of irritant reactions occur within 48 h of exposure. One exception to this is in patients with sensitive skin types (e.g., newborn, filaggrin mutation, and the elderly) who can become chronically irritated by low-grade irritants, such as soap [1]. The mainstay of treatment in ICD is cessation of exposure to the offending agent and attention to barrier repair.

Patch testing is the gold standard for confirmatory diagnosis of ACD. There is no current Food and Drug Administration approved pediatric patch test screening kit. The T.R.U.E. Test (SmartPractice, Phoenix, Arizona, USA) is used with higher frequency by pediatric dermatologists than tertiary care center-based comprehensive patch testers [2[•]]. Combined prevalence data of the 2025 children total tested children between the Pediatric Contact Dermatitis Registry and that of the North American Contact Dermatitis Group have been incorporated into a list of the top 40 allergens (Table 1) [3]. The

top prevalence allergens that would have been missed by failure to screen using the T.R.U.E. Test are bolded in Table 1.

As with adults there are those allergens, which may be regionally less prevalent due to usage patterns, as in neomycin in Europe, where the allergen is not widely available over-the-counter. For this reason, a comprehensive history directing the allergen selection in children can be fruitful. Current evidence suggests that children over 6 years may be safely and efficaciously tested with the same allergen concentrations as adults [4]. Some centers recommend removal of the patch tests at 24 h, whereas others advocate for a 48-h removal [5]. Irritant reactions have been reported in very young patients and patients with barrier deficiencies, and in these cases, some investigators suggest adjustments in allergen concentration or reduction of exposure interval be made [6].

DISCUSSION

In 2014, Jacob *et al.* [7] developed a basic 20-allergen pediatric patch test screening series, and comparative analysis of the 20-allergen screen against the current top 40 pediatric allergens revealed that the 20-allergen screening series would have theoretically only captured 47.5% ($n=19$) of the relevant contact allergens (aka a 52.5% failure to detect rate). Furthermore, the T.R.U.E. Test would have hypothetically captured 60% ($n=24$) of the top 40 allergens (aka a 40% failure to detect rate). This highlights the importance of being aware of the potentially significant allergens that may be missed by screening with a basic screening kit or series.

Patch testing does have limitations, some based on the experience of the practitioner in the diagnostic test (e.g., correct allergen selection, reading of the test, and assignment of relevance), whereas others are based on the complex nature of the skin function as an immunologic organ, both of which affect the sensitivity of the test. For example, Correa da Rosa *et al.* [8] reported that global attenuation and differential polarization exists in patients with atopic dermatitis, with significant decreases in levels of TH1 cytokines, some increases in levels of TH17 cytokines, and inconsistent upregulation in levels of TH2 products. There was an increased expression of inflammatory products, such as T-cell trafficking markers (CCR7), interferon/TH1-related genes (*IFN-alpha*, *IFN-gamma*, *CXCL9*, and *CXCL11*), and TH17/IL-23-related genes (*IL-12/23p40* and *CCL20*) [8]. This immune system skewing could potentially lead to an overall hyporesponsiveness in skin from patients with background atopic dermatitis leading to false negative reactions in truly affected persons.

Table 1. Top 40 allergens prevalence rates

	Allergen	Prevalence (%) 2016
1.	Nickel sulfate 2.5% pet	24.24
2.	Cobalt chloride 1% pet	10.40
3.	Fragrance mix I 8% pet	8.34
4.	Balsam of peru (myroxylon pereirae) 25% pet	7.13
5.	Neomycin sulfate 20% pet	7.05
6.	Bacitracin 20% pet	5.67
7.	Gold sodium thiosulfate	5.52
8.	Wool (wax) alcohols 30%	4.73
9.	Formaldehyde 1% aq	4.43
10.	Methylisothiazolinone 0.2% aq	4.29
11.	Bronopol (2-bromo-2-nitropropane-1,3-diol) 0.5% pet	3.81
12.	Propylene glycol 30% aq	3.77
13.	Methylchloroisothiazolinone/methylisothiazolinone 0.01%	3.50
14.	Quaternium-15 2% pet	3.42
15.	Fragrance mix II 14% pet	3.30
16.	Amerchol-L101-lanolin alcohol 50% pet	3.24
17.	Cocamidopropyl betaine 1% aq	3.23
18.	Potassium dichromate 0.25% pet	3.18
19.	Carba mix 3% pet	2.95
20.	p-Phenylenediamine 1% pet	2.72
21.	Decyl glucoside 5% pet	2.70
22.	Disperse blue	2.67
23.	Propolis 10% pet	2.55
24.	p-tert-Butylphenol formaldehyde resin	2.34
25.	Colophony 20% pet	2.17
26.	Compositae mix 6% pet	2.17
27.	Iodopropynyl butylcarbamate 0.5% pet	1.95
28.	Black rubber mix	1.87
29.	Tixocortol-21-pivalate 1% pet	1.84
30.	Thiuram mix	1.67
31.	Sorbitan sesquioleate 5% pet	1.66
32.	Cinnamic aldehyde 1% pet	1.60
33.	Methyldibromoglutaronitrile/phenoxylethanol 2% pet	1.59
34.	Diazolidinyl urea 1% pet	1.42
35.	Dimethylaminopropylamine 1% aq	1.38
36.	Paraben mix 12% pet	1.28
37.	DI alpha tocopherol 100%	1.24
38.	Parthenolide	1.23
39.	Mercaptobenzothiazole 1% pet	1.09
40.	Amidoamine 0.1% aq	1.06

Key: Thiomersal had a prevalence rate of 3.06 and was not included on this table due to its low relevance. The high rate of paraphenylenediamine (2.72) likely reflects hair dyeing practices of older teen females, in addition to exposure through black henna tattooing practices. As this allergen is a strong sensitizer, it should not be tested unless history warrants under 12. The top prevalence allergens that would have remained undetected by screening with the T.R.U.E. Test are bolded.

The challenges of evaluation of ACD in atopic dermatitis speak volumes to the observance of these immune shifts and provocations. It is notable, that the current evidence suggests the sensitivity and specificity of patch testing is 70 and 80%, respectively [9]. The specificity of the test is highly dependent on the correct selection of the haptens to be evaluated and for that matter the correct reading time of that hapten (e.g., early, delayed, and late delayed presenters). Epoxy, gold, and thimerosal are examples of allergens which have been shown to have low relevance as general screening agents in children and should only be tested for as warranted by history [7,10].

Photoallergens and photoallergic reactions

False negative reactions may also occur if standard patch testing is utilized in the case where the allergen is a photoactivated chemical – a ‘photoallergen’. These agents require the additional factor of ultraviolet-A (UVA) radiation to be present at the point the agent is in contact with the skin to elicit photoallergic contact dermatitis (PACD). Therefore, the detection of PACD requires the addition of UVA irradiation to standard patch testing methodology, an investigation termed photopatch testing. The two main groups of agents that can lead to PACD are organic sunscreen absorbers and topical NSAIDs. A consensus methodology for photopatch testing has existed for over a decade [11] and a proposed ‘baseline’ photopatch test series for adults in Europe has been suggested [12]. No such baseline series currently exists for children, although one based on the adult series has recently been postulated as a practical solution, taking into account issues specific to children, not least of which is physical space on the skin of the back (Table 2) [13].

It can be seen that topical NSAIDs are not present in Table 2, which consists of ‘older’ and ‘newer’ organic sunscreen absorbers. In children, photopatch testing to topical NSAIDs is warranted only if there is a clear history of use in the child. The specific topical NSAIDs piroxicam, diclofenac, and ibuprofen can be tested in pet at concentrations of 1, 5, and 5%, respectively, if indicated.

Topical ketoprofen (a propionic acid class NSAID) has been shown to be a more potent photoallergen than the other NSAIDs and organic ultraviolet absorbers and appears to potentially coreact with the two organic absorbers benzophenone-3 and octocrylene [14]. Furthermore, there is evidence that ketoprofen’s photodegradation products are potentially more photosensitizing than the drug itself [15]. Because of these properties, it may be advisable not to photopatch test children to topical ketoprofen, unless there is specific indication.

Table 2. A possible ‘baseline’ children’s photopatch test series^a

Type of agent	International Nomenclature of Cosmetic Ingredients name	United States Adopted Name	Concentration/vehicle
N/A	Patient’s own sunscreen	N/A	‘As is’
‘Older’ organic UV absorbers	Octocrylene	Octocrylene	10% pet
	Benzophenone-3	Oxybenzone	10% pet
	Butyl methoxydibenzoylmethane	Avobenzone	10% pet
	Isoamyl- <i>p</i> -methoxycinnamate	Amiloxate	10% pet
	Ethylhexyl methoxycinnamate	Octinoxate	10% pet
	Benzophenone-4	Sulisobenzone	2% pet
	4-Methylbenzylidene camphor	Enzacamene	10% pet
‘Newer’ organic UV absorbers	Methylene bis-benzotriazolyl tetramethylbutylphenol	Bisotrizole	10% pet
	Diethylamino hydroxybenzoyl hexyl benzoate	N/A	10% pet
	Ethylhexyl triazone	N/A	10% pet
	Bis-ethylhexyloxyphenol methoxyphenyl triazine	Bemotrizinol	10% pet
	Drometrizole trisiloxane	N/A	10% pet

UV, ultraviolet.
^aSome of the ‘newer’ sunscreen agents were not approved at the time of submission for use as sun screening agents and readers are advised to consult the most current Food and Drug Administration advice if doubt exists.

As with conventional patch testing, one should also remain vigilant to the possibility of new photoallergens emerging and photopatch test agents of suspicion when felt clinically safe and justified [16]. Notably, in a recent presentation on nine cases of photoaggravation and persistent photosensitivity in patients sensitized to methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone in Belgium and France, a patient was found to have PACD to methylisothiazolinone, whereas two patients had reduced UVB minimal erythema doses subsequently, suggesting the development of chronic actinic dermatitis syndrome subsequent to florid isothiazolinone-based ACD [17].

MANAGEMENT

The remission state for contact dermatitis is dependent on the ability to both detect and avoid the exogenous offending haptens. In the case of ICD, the diagnosis is primarily made through history and exam. The crux of treatment should focus on both repair and restoration of the skin barrier function (with emollients), in combination with preventing further contact with the culprit agent. With ACD, the mainstay of treatment included such measures as well as avoiding the inciting agent while instituting measures to subdue inflammation (with compresses, topical corticosteroids, and/or topical immunomodulators). For a comprehensive review of therapeutic options, the readership is directed to the American Contact Dermatitis Society website (www.contactderm.org), the Dermatitis Academy

website (www.dermatitisacademy.com), and key reference articles [18,19].

PREVENTION AND PREEMPTIVE AVOIDANCE STRATEGY

As discussed previously, the sensitivity of the test is defined by the ability to detect-confirm the inciting hapten. Regardless, of the practitioners experience level, if the inciting agent is not suspected and thus not tested for, it will remain elusive, and the patient may be misdiagnosed or opted into systemic immunosuppressive therapies. Through review of the top haptens affecting children in the two large multicenter trials a top 40 list was derived, which includes allergens with a current prevalence rate above 1.0%. Utilizing this list of allergens portends a greater chance of correct confirmatory diagnosis in a majority of cases.

Pre-Emptive Avoidance Strategy has been suggested for patients with minimal access to patch testing or in those with widespread dermatitis in which performing patch testing may present unique challenges [18,19]. Avoidance of the known top offending allergens can lead to significant clinical improvement in at least 25–30% of the cases. Likewise, decreased utilization of these top offenders by consumers and manufacturers would impact sensitization rates.

CONCLUSION

Contact dermatitis is an economically burdensome pediatric disease that leads to significant health and social ramifications for both the pediatric patient and

their caregivers. In the last 15 years, patch testing in children has been more commonly practiced and, as is the case in adults, management requires the identification and elimination of the offending hapten from the sensitized person's environment. Given that there are a significant number of allergens that have remained top offenders for well over the last decade, preemptive avoidance of these known allergens is prudent. These known allergens should also be appropriately monitored and may remain potential targets for legislative regulation. That said, it is important to continue to maintain a watchful eye for new emerging allergens in the environment.

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Conflicts of interest

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