

ORIGINAL ARTICLE

Both children and adult patients with difficult-to-treat atopic dermatitis have high prevalences of concomitant allergic contact dermatitis and are frequently polysensitized

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Abstract

Background Concomitant allergic contact dermatitis (ACD) has been described as a possible cause of atopic dermatitis (AD) becoming difficult-to-treat. However, contact sensitization in this patient group has barely been studied.

Objective To study the occurrence of ACD in a population of difficult-to-treat AD children and adults.

Methods Clinical and patch test information of 48 patients with difficult-to-treat AD unresponsive to conventional outpatient treatments was gathered retrospectively. We studied prevalence and relevance of common allergens, performed dynamic patch test analysis and assessed occurrence of polysensitization.

Results In 48 patients with difficult-to-treat AD, 75% ($n = 36/48$) had a concomitant contact allergy, and 39% ($n = 14/36$) of these patients were polysensitized. ACD and polysensitization prevalences were equal amongst children and adults. The most frequent and relevant reactions were seen against wool alcohols, surfactants cocamidopropyl betaine and dimethylaminopropylamine, bichromate and fragrance mix I. Dynamic pattern analysis showed these reactions to be mostly allergic and not irritative of nature.

Conclusion Difficult-to-treat AD patients frequently suffer from concomitant (multiple) contact allergies, and this may be a reason why the AD turns into a difficult-to-treat disease. Awareness of this phenomenon is necessary, as pragmatic implementation of allergen avoidance strategies may be helpful in getting disease control in this population.

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Conflicts of interest

The authors have no funding or conflict of interests to declare.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease characterized by pruritic erythematous scaly lesions and dryness of the skin. The majority of patients with AD are treated in an outpatient setting, where the mainstay of therapy is focused on basic skin care with moisturizers and topical treatments with steroids and immunosuppressants. However, in some cases, patients with AD are refractory to these conventional treatments, making it a difficult-to-treat disease. Several authors have reviewed the subject of difficult-to-treat or difficult-to-control AD, stating diverse possible explanations for the problem, such as lack of compliance,¹ psychosocial factors,^{2,3} skin infections,^{4,5} exacerbations triggered by food and aeroallergens,^{6–8} and concomitant allergic contact dermatitis (ACD).^{9–11} All these factors may contribute to making the disease difficult-to-treat.

Historically, patients with AD were thought to be less prone to develop ACD, because of a decreased cell-mediated

immunity.^{12,13} Recent studies, however, show that atopic individuals are at least as likely to develop ACD compared to non-atopic individuals.^{14–21} Additionally, lack of functional filaggrin has been shown to increase the risk of ACD in patients with AD.^{22,23}

As can be expected from frequent exposition to allergens in topical therapy, allergies to lanolin alcohols and antiseptics occur regularly within patients with AD.^{21,24} Several specific allergic contact reactions are described to occur more often in AD children compared to healthy children. A large multicentre study in Dutch children showed that children with AD were significantly more often sensitized to fragrances and wool alcohols.²¹ Also, potassium dichromate, disperse blue 106 and compositae mix are frequent sensitizers.²⁵ If corticosteroid therapy is not sufficient for treating AD anymore, many dermatologists may suspect an allergy for corticosteroids.^{24,26,27}

We investigated the occurrence of a concomitant ACD in a population of difficult-to-treat AD patients, which had to be

admitted to a specialized day care treatment unit for AD because of unresponsiveness to conventional outpatient treatments. This study aims to (i) determine the rate of ACD in this population of difficult-to-treat AD, (ii) identify the most common allergens and determine their allergic and irritative properties by dynamic patch test analysis and (iii) determine the rate of polysensitization in this population.

Materials and methods

Patients

We performed a retrospective analysis of 190 patients with a clinical diagnosis of AD that had been seen between November 2012 and February 2015 at the Academic Medical Center (AMC) day care treatment centre because of difficult-to-treat AD. The UK Working Party criteria²⁸ were retrospectively applied to all patients. Forty-eight patients were excluded because they did not meet diagnostic criteria. Of the 142 patients having the diagnosis of AD according to the UK Working Party criteria (UK+ patients), 69 patients ($n = 69/142$; 49%) were referred for patch testing because of suspected ACD, but 51 patients ($n = 51/142$; 36%) actually underwent patch testing. Only patch test series applied in at least 50% of tested patients were included for analysis. These were the European Baseline Series (EBS; $n = 45/51$; 88%), a routine supplementary series ($n = 42/51$; 82%), wool alcohol series ($n = 40/51$; 80%) and corticosteroid series ($n = 35/51$; 69%; Table 1). Two UK+ patients ($n = 2/51$) were not tested with any of these series and were therefore excluded from further analysis. Additionally, one UK+ patient in which EBS was applied, had an angry back at time of the readings and was therefore not included in further analysis. This study will therefore discuss patch test results of 48 UK+ patients (48/142; 34%) tested with the abovementioned patch test series. In patients with full body pictures available, eczema area and severity index score (EASI) were determined in retrospect by two experienced observers.

Patch tests

Patients were routinely tested with the EBS and a routine supplementary series unless contraindicated, and with additional patch test series depending on the patient's history and physical examination. Patch tests were performed with van der Bend square chambers (van der Bend, Brielle, The Netherlands) in combination with allergens from Almirall (Reinbek, Germany) or Chemotechnique (Vellinge, Sweden), or the TRUE Test[®] (SmartPractice Denmark, Hillerød, Denmark). Readings were performed on day (D) 2 and D3. The reactions were scored according to the recommendations of the ICDRG and ESCD.²⁹ The clinical relevance was determined for each positive patch test result. Clinical relevance was scored as follows: 'definite' when the clinician was 100% convinced that the allergen was causative for the dermatitis, the patient was exposed to the

Table 1 Administered patch test panels to 51 UK+, difficult-to-treat atopic dermatitis patients

Test series	n (%)
European baseline series	45 (88%)
Corticosteroids, including the solvent DMSO	35 (69%)
Epoxy resins	1 (2%)
Essential oils	3 (6%)
External drugs	5 (10%)
Glues	1 (2%)
Parabens	8 (16%)
Beta-lactams	1 (2%)
Perfumes	3 (6%)
Photo-contact allergens	1 (2%)
Rubber accelerators	4 (8%)
Shoe ingredients	4 (8%)
Supplementary series	42 (82%)
Textile dyes	4 (8%)
TRUE test	6 (12%)
Titanium salts	1 (2%)
Wool alcohols	40 (80%)

UK+, meeting UK Working Party criteria.

allergen, the allergen was present in the environment of the patient, and sites of dermatitis had a clear relationship with the allergen-containing product; 'probable' when there was a strong relationship between the allergen and dermatitis; 'possible' when the relationship between the allergen and dermatitis was less clear, but the allergen was nevertheless suspected to have caused ACD; and 'unlikely-not/uncertain' when ACD was not suspected. Relevance scores provided in this article refer to 'definite' and 'probable' relevance scores, and of current relevance. This study was exempt from medical ethics committee approval.

Data analysis

To determine the prevalence of positive patch tests (PPT) to the allergens in the investigated series (EBS, routine supplementary series (Table 2), wool alcohol series and corticosteroid series), we divided the positive reactions per allergen by the total number of times that the allergen was tested (PPT%).

To identify the allergens that were both the most common and the most relevant, we multiplied the prevalence with the relevance score of 'definite' and 'probable', current relevance, obtaining the percentage of clinically relevant patch tests (RPPT%).

As patch testing in patients with AD is challenging because of an increased risk of irritant patch test reactions, dynamic patch test analysis has also been performed.^{30,31} Dynamic patch test analysis shows how a patch test reaction evolves over several days (from D2 to D3 readings), whereby crescendo and plateau reactions are considered to be truly allergic reactions, and decrescendo reactions are considered to be irritant reactions.

Table 2 Allergens of routine supplementary series

Disperse blue 106
Diazolidinyl urea
1,2-benzisothiazolin-3-one sodium salt
Imidazolidinyl urea
Turpentine peroxide
2-bromo-2-nitropropane-1,3-diol
Carbamix
Ethylenediamine-di-HCl
Thiomersal
Amerchol L101
p-toluenesulfonamide
Cocamidopropyl betaine
Hydrocortisone-17-butyrate
2-n-octyl-4-isothiazolin-3-on
Iodopropynyl butylcarbamate
Sorbitansesquioleate
2-phenoxyethanol
Methylisothiazolinone
Tixocortol pivalate
Benzophenone-4
Sodium metabisulfite
Propyl gallate
Dimethylaminopropylamine

We also determined the amount of polysensitization present in this population of difficult-to-treat AD. Polysensitization was defined as an allergic reaction to three or more unrelated contact allergens.^{32,33} Analysed allergens were grouped together according to cross-reactivity, concomitant exposure, and releasers of similar compounds, as for example in formaldehyde releasers (Table S1). A patient was considered polysensitized in case the patient reacted to at least three different groups of allergens.

All statistical analyses were performed in SPSS[®], software version 21.0 (SPSS, Inc., Chicago, IL, USA). Distribution was tested by Q–Q plot and Kolmogorov–Smirnov or Shapiro–Wilk test depending on sample size. Continuous variables are presented as mean (standard deviation) or median [interquartile range (IQR)] according to their distribution.

Results

Rate of ACD in difficult-to-treat AD

Of the 48 UK+ patients analysed, the median age was 14.6 years (IQR: 10.1–19.0), of which 71% were children ($n = 34/48$) and 29% were adults ($n = 14/48$), with 44% ($n = 21/48$) being male. Mean EASI score was 25 (IQR: 12–41; available in 26/48 patients). We found that 75% ($n = 36/48$) of patients had at least one positive patch test, of which 67% ($n = 24/36$) were children (age below 18 years) and 33% ($n = 12/36$) were adults. In these 36 patients, the median age [median 15.2 years (IQR: 10.8–20.6; range: 4.2–54.6 years), $P = 0.396$] and number of

males (44%, $n = 16$, $P = 0.563$) did not differ from the 48 UK+ patients.

Most common allergens and relevance

Table 3 shows PPT% en RPPT% of the most common sensitizers in the total population, as well as for children and adults separately. The ten most frequent allergens in the total population were bichromate ($n = 12/44$, PPT 27%) and nickel ($n = 12/44$, PPT 27%), wool alcohols ($n = 10/41$, PPT 24%), cocamidopropyl betaine (CAPB; $n = 10/44$, PPT 24%), amerchol L101 ($n = 11/47$, PPT 23%), wollwachsalkoholsalbe DAB9 (German wool wax emollient, containing 75% wool wax and 25% water; $n = 10/44$, PPT 23%), cremor lanette ($n = 7/40$, PPT 18%), dimethylaminopropylamine (DMAPA) ($n = 7/42$, PPT 17%), cobalt ($n = 5/44$, PPT 11%) and eucerine cum aqua ($n = 4/40$, PPT 10%). Relevance scores (current ‘definite’ and ‘probable’ relevance) were 100% for all allergens except for bichromate (43%), nickel(II)-sulphate (13%) and cobalt (33%).

The RPPT% shows that fragrance mix I ($n = 4/44$, PPT 9%, RPPT 9%) and unguentum lanette ($n = 3/40$, PPT 8%, RPPT 8%) are allergens that when positive, are more important in explaining clinical findings than nickel and cobalt, which in RPTT% rank 17th and 21st, respectively. This shows that although nickel and cobalt are common allergens, they are seldom considered to be of current relevance in this AD population.

Dynamic pattern analysis

Results of dynamic pattern analysis can be found in Table 4. Bichromate and fragrance mix I are the only allergens in which allergic reactions also occurred as being decrescendo. This means that only in bichromate and fragrance mix I, positive patch tests can indicate irritative reactions instead of truly allergic reactions. All other allergens display plateau and crescendo patterns, indicating true allergic reactions.

Additionally, in wool alcohols, amerchol L101 and fragrance mix I (data not shown), a doubtful positive reaction was seen on D2; however, all these reactions developed to a ‘+’ reaction. In contrast, in cremor lanette, DMAPA and eucerine cum aqua all doubtful positive D2 reactions disappeared at the later reading.

Polysensitization

Polysensitization was present in 39% ($n = 14/36$) of sensitized patients. There was no difference in the age of patients monosensitized (median age 16.3 years; IQR: 10.9–21.4) or polysensitized (median age 13.9; IQR: 10.1–24.9; $P = 0.51$).

Polysensitization occurred to three or four groups of allergens (both $n = 5$, 36%), as well as to five or more allergen groups ($n = 4$, 29%). In polysensitized patients, the most common allergen groups to which sensitization occurred were wool alcohols ($n = 10/14$, PPT 71%), followed by metals and preservatives

Table 3 Most common positive patch test results in 48 UK+ difficult-to-treat atopic dermatitis patients: Top 10 allergens and additional allergens according to relevant positive patch tests

	Total group (n = 48)				Children (0–17 years) (n = 34)				Adults (18+ years) (n = 14)					
	Tested	PPT	RPPT*	Patients sensitized	Tested	PPT	RPPT*	Age Median (IQR)	Tested	PPT	RPPT*	n	%(n)	%
	n	%(n)	%		n	%(n)	%		n	%(n)	%			
1) Bichromate	44	27 (12)	12	14 (10–17)	42 (5)	1) Amerchol L101	30	37 (11)	37	1) Nickel(II)-sulphate	14	29 (4)	0	
2) Nickel(II)-sulphate	44	27 (12)	3	15 (10–22)	67 (8)	2) Bichromate	30	33 (10)	14	2) Cocamidopropyl betaine	14	21 (3)	21	
3) Wool alcohols	41	24 (10)	24	14 (10–16)	30 (3)	3) Wool alcohols	30	30 (9)	30	3–12) Bichromate	14	14 (2)	14	
4) Cocamidopropyl betaine	42	24 (10)	24	16 (12–25)	50 (5)	4) Nicke(II)-sulphate	30	27 (8)	5	3–12) Caine-mix III†	14	14 (2)	0	
5) Amerchol L101	47	23 (11)	23	11 (10–15)	36 (4)	5) Wollwachsalkoholsalbe DAB9‡	30	27 (8)	27	3–12) Wollwachsalkoholsalbe DAB9‡	14	14 (2)	14	
6) Wollwachsalkoholsalbe DAB9‡	44	23 (10)	23	11 (9–17)	20 (2)	6) Cocamidopropyl betaine	28	25 (7)	25	3–12) Fragrance mix I	14	14 (2)	14	
7) Cremor lanette§	40	18 (7)	18	15 (10–15)	29 (2)	7) Cremor lanette§	29	24 (7)	24	3–12) 2-n-octyl-4-isothiazolin-3-one	14	14 (2)	14	
8) Dimethylaminopropylamine	42	17 (7)	17	12 (11–21)	29 (2)	8) Dimethylaminopropylamine	28	18 (5)	18	3–12) Iodopropynyl butylcarbamate	14	14 (2)	14	
9) Cobalt(II)-chloride	44	11 (5)	3	11 (10–17)	60 (3)	9) Eucerine cum aqua¶	30	13 (4)	0	3–12) Sorbitansesquiolate	14	14 (2)	0	
10) Eucerine cum aqua¶	40	10 (4)	10	11 (10–14)	0 (0)	10) Cobalt(II)-chloride	29	14 (4)	14	3–12) Benzophenone 4	14	14 (2)	14	
Add 1. Fragrance mix I	44	9 (4)	9	24 (6–51)	50 (2)	Add 1. Unguentum lanette	28	7 (2)	7	3–12) Sodium metabisulfite	14	14 (2)	7	
Add 2. Unguentum lanette	40	8 (3)	8	11 (10–13)	33 (1)	Add 2. Dimethylaminopropylamine	14			3–12) Dimethylaminopropylamine	14	14 (2)	14	
						Add 1. Wool alcohols				Add 1. Wool alcohols				

*RPPT: relevant positive patch test; to obtain a rate for allergens that were both the most common and the most relevant, we multiplied the prevalence (PPT%) with the relevance score of 'definite' and 'probable', current relevance, obtaining the percentage of clinically relevant patch tests (RPPT%).

†Caine-mix III: Benzocaine, Dibucaine-HCl (cinchocaine), and Tetracaine-HCl (amethocaine).

‡Wollwachsalkoholsalbe DAB9: German wool wax emollient (75% wool wax and 25% water).

§Cremor lanette: 10% cetostearyl alcohol, 1% sodiumlaurylsulphate, 14% cetiol V, 3% sorbitol 70%, 0.1% sorbic acid, 72% H₂O.

¶Eucerine cum aqua: 56% white petrolatum, 3.5% wool alcohols, 0.5% cetylstearyl alcohol, 40% H₂O.

Add, additional allergens represent allergens that would rank in the top 10 according to RPPT%; PPT, positive patch test; UK+, atopic dermatitis meeting UK Working Party criteria.

Table 4 Dynamic pattern analysis of the 10 most common and relevant allergens (highest RPTT%) in 48 UK+ difficult-to-treat atopic dermatitis patients

	Total <i>n</i>	Crescendo % (<i>n</i>)	Plateau % (<i>n</i>)	Decrescendo % (<i>n</i>)
Wool alcohols	10	100 (10)	0 (0)	0 (0)
Cocamidopropyl betaine	10	90 (9)	10 (1)	0 (0)
Amerchol L101*	15	87 (13)	13 (2)	0 (0)
Wollwachsalkoholsalbe	10	80 (8)	20 (2)	0 (0)
Cremer lanette	7	86 (6)	14 (1)	0 (0)
Dimethylaminopropylamine	7	71 (5)	29 (2)	0 (0)
Bichromate†	11	9 (1)	55 (6)	36 (4)
Eucerine cum aqua	4	75 (3)	25 (1)	0 (0)
Unguentum lanette	3	67 (2)	33 (1)	0 (0)
Fragrance mix I	4	50 (2)	25 (1)	25 (1)

*Amerchol L101 was present in the wool alcohol series and in routine supplementary series; therefore, some patients were tested more than once.

†In one patient with a positive test, patch test reading was performed only on day 2; this patient could therefore not be included in dynamic patch testing.

UK+: meeting UK Working Party criteria.

Dynamic pattern analysis was carried out amongst all patients with readings on D2 and D3, with a positive reading on either of these days, non-follicular and non-irritative; therefore, the *n* does not represent all patients tested, but only positive readings.

Table 5 Sensitization prevalences of allergen groups* within 14 polysensitized UK Working Party criteria difficult-to-treat AD patients

Allergen group*	<i>n</i> (%)
Wool alcohols	10 (71)
Metals	9 (64)
Preservatives	9 (64)
Surfactants	6 (43)
Fragrances	6 (43)
Rubbers	4 (29)
Local anaesthetics	3 (21)
Corticosteroids and DMSO	3 (21)
Sorbitan sesquioleate	2 (14)
p-phenylenediamine (PPD) and PPD-like agents	2 (14)
Epoxy resins	1 (7)
Formaldehyde and formaldehyde releasers	1 (7)
Antioxidants	0 (0)
Antibiotics	0 (0)
Clioquinol	0 (0)
Composites	0 (0)
Ethylenediamine	0 (0)
p-tert-butylphenol	0 (0)
Primin	0 (0)

*Grouping of allergens is based on cross-reactivity, concomitant exposure and releasers of similar compounds.

(both *n* = 9/14, PPT 63%; Table 5). Within polysensitized patients, of the wool alcohol group, amerchol L101 was the allergen that was positive most often (*n* = 7/13, PPT 54%), within metals these were nickel (*n* = 5/13, PPT 36%) and bichromate (*n* = 5/14, PPT 36%) and within preservatives benzophenone-4 (*n* = 4/14, PPT 29%; data not shown).

Discussion

This study shows that ACD and polysensitization are frequent within difficult-to-treat AD patients. The group composition of the population under study is dominated by children, with only a quarter of patients having reached adult age. A recent large study conducted in three University Hospitals in The Netherlands, including our centre, showed that 48% of children with AD who were tested based on clinical suspicion had one or more positive patch test reactions compared to 47% of children without AD.²¹ In the current study, we found a sensitization rate of 71% (*n* = 24/34) in children and 86% (*n* = 12/14) in adults amongst 48 difficult-to-treat AD patients. This prevalence in children is much higher than in the previously mentioned study by Lubbes *et al.*²¹ and exceeds the prevalence of 30% in AD children and adolescents reported by Simonsen *et al.*³⁴ Our findings reflect the higher prevalence of ACD in this selected difficult-to-treat AD patient group as compared to patients with AD patch tested due to clinical suspicion during routine outpatient care or to screen for contact allergies. The mean EASI of 25 shows that this is indeed a group of severe AD patients,³⁵ which makes it a different subgroup compared to mild AD patients, with therefore different rates of contact sensitization.

It has been shown that in a general population patch tested because of ACD suspicion, one of every six to seven ACD patients (14–16%) had multiple allergies.³⁶ The amount of polysensitization we found exceeded this number. However, AD is a known risk factor for polysensitization, and polysensitized patients with AD have been shown to have a more persistent dermatitis,³² which may explain the high number of polysensitization in our population. More interestingly, also wool alcohol allergy has been associated with polysensitization.³⁷ Although it seems intuitive that severe AD patients having severe impaired

skin barrier would have more penetration of allergens and therefore an increased prevalence of ACD, this is a topic of ongoing discussion.³⁸ As permeability to hydrophilic solutes may increase through imperfection in lipid layers³⁹ and in AD stratum corneum lipid organization is affected,⁴⁰ this may increase permeability of hydrophilic zwitterionic surfactants such as CAPB and DMAPA. Additionally, other surfactants, such as present in wool alcohols, may also increase penetration of other compounds.⁴¹ Also, the influence of emollients on the skin microbiome^{42,43} could change the tolerance against several allergens⁴⁴ making frequent emollient applicators more prone to ACD. For this subject, however, more detailed research is warranted.

Experimental settings show an inverse relationship between AD and ACD, hypothetically because of antagonistic influences of Th1 (ACD) and Th2 (AD). More recent research, however, indicates that ACD cannot be a single entity, and the murine model of sensitization does not self-evidently apply to the human situation. For example, wherein the murine model ACD was induced by a potent sensitizer, dinitrofluorobenzene, human ACD can also be elicited by less potent sensitizers, such as nickel, which do not induce ACD in mice.⁴⁵

Most positive reactions were seen against metals, wool alcohols and surfactants, but when taking relevance into account, the 10 most frequent allergens are made up by wool alcohols, surfactants (CAPB and DMAPA), bichromate and fragrance mix I. There is much debate about whether positive patch test reactions to wool alcohols and CAPB/DMAPA are truly allergic or mainly irritative in patients with AD.⁴⁶ For this reason, we performed dynamic pattern analysis, which shows that reactions to wool alcohols and CAPB/DMAPA have an allergic rather than an irritant pattern, indicating true allergic reactions.

Sensitization to wool alcohols in this population was quite frequent. In previous studies, where only a selected group of wool alcohol derivatives have been tested, lower numbers of wool alcohol sensitization were found.^{14,17,20,26} However, also prevalences of 24% wool alcohol sensitization have been reported previously.⁴⁷ In our study, patients were tested with a wool alcohol series, which may lead to a better detection of wool alcohol allergies. The high number of wool alcohol sensitization found in our population may also be inherent to the studied population of difficult-to-treat AD itself. One of the reasons why this population may be 'difficult-to-treat' may in fact be the direct result from their concomitant contact allergy to wool alcohols, which are frequently present in emollients as well as in therapeutic ointments prescribed by dermatologists. The very medication intended to treat the AD may actually be eliciting an ACD, clinically mimicking an AD flare. If gone unrecognized, this may result in a vicious circle of increased use of topical treatments eliciting more dermatitis, ultimately resulting in a case of difficult-to-treat 'AD'. Important to note is that of the 48 patients excluded from further analyses because of not meeting UK Working Party criteria, the nine patients ($n = 9/48$) who

were patch tested, all had a contact allergy. These patients were all clinically diagnosed with AD but did not meet the diagnostic criteria for AD retrospectively. One could speculate that these patients may have been clinically misdiagnosed as AD, and actually had an ACD instead, but this was not further investigated.

Another interesting finding is the high prevalence and relevance of reactions to surfactants CAPB/DMAPA. As the presence of these surfactants is frequent in daily cosmetic products (shampoo, liquid soap, toothpaste), sensitization to the agents could easily occur. High prevalences of CAPB/DMAPA contact allergies have been found by other authors as well, but are underreported as they are often not tested, as they are not in the EBS and only tested on indication.^{25,48,49} The allergenic potential of CAPB has been disputed, and it is argued whether CAPB is a true allergen or only an irritant.⁵⁰ As CAPB and DMAPA only show crescendo and plateau patterns in our dynamic pattern analysis, we think that at least in this population they reflected true allergic reactions.

As we studied an AD population with recalcitrant disease, we had expected more allergic reactions to corticosteroids. Especially, group A corticosteroid allergy has been associated with AD.⁵¹ Probably, in recalcitrant AD disease, exposure to group A corticosteroids is lower and group B–D corticosteroids are prescribed more often. However, we did not find these reactions in our study population.

Based on our results, we would advise to have a high level of suspicion and readily patch test patients with difficult-to-treat AD as part of their diagnostic workup. A frequent problem encountered by dermatologists treating these patients is that patch testing cannot be performed due to the active dermatitis, and therefore, contact allergies will not be detected in this group. However, in our experience, by putting the patients on a strict regimen of usage of only toiletries and topical treatments free of wool alcohols, CAPB/DMAPA and fragrances, combined with adequate topical anti-inflammatory treatment, frequent use of emollients and regular use of bleach baths, these patients can usually be tested within 6–12 weeks. This usually is easier to achieve in children, as they do not yet need as many toiletries as adults.

The main limitations of this study are its retrospective nature and its relative small sample size. Not all patients with difficult-to-treat AD were tested systematically, as testing was performed only based on clinical suspicion. EASI scores were not available in all patients. Other less frequently tested relevant allergens were not studied. Other causes for why the AD was difficult-to-treat, for instance possible lack of functional filaggrin, were not explored in this study.

In conclusion, we found high rates of concomitant ACD and polysensitization in a population of difficult-to-treat AD children and adults. The most frequent and relevant reactions were seen against wool alcohols, surfactants such as CAPB and DMAPA, bichromate and fragrance mix 1. Dynamic pattern

analysis indicates that these reactions were allergic and not irritative of nature. Based on these results, avoidance of contact with these allergens seems to be advisable for patients with difficult-to-treat AD. More research into wool alcohol ACD within patients with AD is warranted, as current prescription habits seem effective,⁵² although their role in the development of difficult-to-treat AD and polysensitization is unclear for the AD population in general.

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Author contributions

MMH and TR conceived of the presented idea. MB performed the data collection and analysis. MMH and TR helped with interpretation of the results. MB wrote the paper, with input from MMH and TR for the final manuscript.

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Supporting information

Additional Supporting Information may be found online in the supporting information section at the end of the article:

Table S1. Grouping of allergens according to cross-reactivity, concomitant exposure and releasers of similar compounds.