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Contact sensitization in pediatric patients with atopic dermatitis: a purpose for a new patch testing series for the Portuguese population

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Key words

Atopic dermatitis; allergic contact dermatitis; prevalent allergens; baseline series; pediatric patients.

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Impact statement

Children with and without atopic dermatitis have similar contact sensitization rates however to different allergens. An adapted baseline series with the most relevant allergens is proposed for the pediatric population with atopic dermatitis.

Summary

Background. *Atopic dermatitis is a prevalent condition in the pediatric population, with affected children exhibiting a susceptibility to cutaneous sensitization due to skin barrier dysfunction and immune dysregulation. Recent studies have highlighted an increased prevalence of certain allergens, which identification may be clinically relevant, with direct implications for the management of atopic dermatitis.* ***Methods.*** *We retrospective reviewed pediatric patients patch tested due to suspected contact dermatitis. Patients were divided according the diagnosis of AD, with subsequent comparison of positive results for both groups.* ***Results.*** *A total of 145 pediatric patch testing were analyzed, 44.1% (n = 63) with the diagnosis of atopic dermatitis. There were notable differences in sensitization rates of relevant allergens between groups and when compared to other European studies. Based on the most prevalent and relevant allergens, we proposed an adapted hapten series for assessing portuguese pediatric patients with AD and suspicion of concomitant allergic contact dermatitis.* ***Conclusions.*** *Our findings confirmed the geographic sensitization variability and emphasize the need for pediatric adaptation and "individualized baseline series".*

Introduction

Atopic dermatitis (AD) is a common illness in pediatric population. In contrast, allergic contact dermatitis (ACD) used to be considered a rarity (1-3). Children with AD are prone to develop cutaneous sensitization due to several factors, due to skin barrier disruption, immune dysregulation, and consequent increased penetration of allergens (1-3). Children with AD are exposed to several allergens from an early age. The frequent application of numerous topical treatments such as emollients and topical drugs may determine a characteristic sensitization profile (1, 3, 4).

Recent studies have shown that sensitization rates are similar between children with and without AD, although certain al-

lergens have a higher prevalence in AD patients. Despite this, the interrelation of AD and ACD is complex, and controversy remains over whether AD increases the risk of contact allergy in children or determines different contact sensitization profiles (1, 2).

Epicutaneous patch testing is the gold standard test for the diagnosis of ACD. It is a specific, relatively inexpensive and safe procedure, even for preschool children however, one of the main limitations is the limited body surface area available for adhesive application (4). Therefore, a selection of allergens based on the exposures and clinical examination are recommended but difficult to standardize (1, 4).

The identification of clinically relevant allergen sensitization in a patient with AD may have important implications for AD disease management and symptom control (3-5). According to the European Academy of Allergy and Clinical Immunology (EAACI) position paper published in 2015 and other recent reviews (1, 4, 6), epicutaneous patch testing is recommended in patients with AD with:

- a suspicion of specific ACD;
- difficult-to-control AD;
- new-onset dermatitis in patients with AD;
- prior to initiating systemic therapy for severe AD.

Considering the difficulty in identifying relevant allergens and their standardization, several research groups have proposed a "baseline series" for the pediatric population, based on sensitization rates in Europe and specific regions (4, 7, 8). Regarding the Portuguese population, few data is available (1, 3), therefore the aim of this study was the creation and subsequent application of a "baseline series" for pediatric AD patients with suspected ACD, difficult-to-control AD, new-onset dermatitis and prior to initiating systemic therapy for AD, or when no specific exposure is identified, in order to improve AD management and treatment in pediatric patients.

Materials and methods

Study design

The authors performed a retrospective, descriptive and inferential review of pediatric patients (< 18 years old) patch tested at the Contact Allergology Unit of the Dermatology and Venereology Department in a tertiary hospital, between 2005 and 2021 (17 years). Patients were divided into two groups: those diagnosed with AD and those without AD, with subsequent comparison of positive results. Based on the analysis of the relevant findings, we proposed an adapted series for assessing portuguese pediatric patients with AD.

All legal guardians of pediatric patients received written informed consent. This paper was written considering the ethical and legal principles and following the recommendations of the Declaration of Helsinki of the World Medical Association. The anonymity of all the participants in this work was guaranteed.

Subjects

Patients were characterized according to demographic data, personal and family history of atopy, and clinical and diagnostic parameters such as allergen series applied, positive reactions, and relevance. Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka (9).

All patients included were routinely tested with the European baseline series and/or with the cosmetic series. The allergens used were from Chemotechnique Diagnostics®, Vellinge, Suécia; Trolab Allergens®, Smartpractice GmBH, Alemanha; Bial Alergénios®. Although, each series has been selected and adapted following the European Society of Cutaneous Allergy and Contact Dermatitis (ESCD) recommendations. Additionally, and in accordance with the available body surface and clinical history, supplementary series or specific allergens were applied. Allergen chambers were from (Epitest Ld®) or IQUltra chambers (Chemotechnique diagnostics®). The allergen chambers were applied on intact upper back and kept in occlusion for 48 hours. Readings were carried out on day(D) 3 or D4, and, in specific cases, associated with a second reading on D7. The reactions were scored according to the recommendations of the International Contact Dermatitis Research Group (ICDRG) and ESCD (10).

It was assessed the sensitization prevalence rates for the population as a whole and stratified for children with and without AD. Allergens patch tested < 20 times were excluded from this analysis to avoid non-inferential results. A value of 20 was chosen to reach a comparable number of patients tested with at least substances in the European baseline series.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 24.0®. Descriptive statistics were analyzed as measures of central tendency and dispersion. The comparison of proportions was made using the chi-square test. Fisher's exact test was used in cases of low sample sizes. A Type I error of 0.05 was considered.

Results

Demographic and clinical characteristics

In a total sample of n = 145 pediatric patients, 68.3% (n = 99) females, with a median 13.0 years old (interquartile range 10-15), corresponding to 4.1% (n = 6) with < 6 years, 35.2% (n = 11) with 6-12 years, and 60.7% (n = 88) with > 12 years, were included in the analysis. AD patients corresponding to 43.4% (n = 63) of the total sample. Patient characteristics are summarized in **table I**.

Table I *- Demographics of pediatric patients referred for Patch Testing due to ACD suspicion.*

Characteristic	Total	With atopic dermatitis	Without atopic dermatitis	P-value
Number, % (n)	100.0 (145)	43.4 (63)	56.6 (82)	
Sex (female), % (n)	68.3 (99)	65.1 (41)	70.7 (58)	0.472
Age (years), median (IQR)	13.0 (10.0-15.0)	12.0 (9.0-14.0)	14.5 (11.0-16.3)	**0.015**
Group age				
< 6 years, % (n)	4.1 (6)	4.8 (3)	3.7 (3)	> 0.99
6-12 years, % (n)	35.2 (51)	44.4 (28)	45.1 (23)	0.467
>12 years, % (n)	60.7 (88)	50.8 (32)	63.6 (56)	0.104
Asthma, % (n)	25.5 (37)	28.6 (18)	23.2 (19)	0.463
Rhinitis, % (n)	25.5 (37)	38.1 (24)	15.9 (13)	**0.02**
Atopy, % (n)	50.3 (73)	76.2 (48)	30.5 (25)	**0.001**
Atopy family history, % (n)	31.7 (46)	42.9 (27)	23.2 (19)	**0.011**
Major location of suspected ACD				
Face, % (n)	40.0 (58)	42.9 (27)	37.8 (31)	0.232
Hands, % (n)	28.2 (41)	17.5 (11)	36.6 (30)	**0.001**
Upper or lower extremities, % (n)	13.1 (19)	12.7 (8)	13.4 (11)	0.648
Generalized, % (n)	6.8 (10)	9.5 (6)	4.9 (4)	> 0.99
Flexures, % (n)	6.2 (9)	7.9 (5)	4.9 (4)	> 0.99
Torso, % (n)	2.8 (4)	3.2 (2)	2.4 (2)	> 0.99
Periumbilical, % (n)	2.8 (4)	6.3 (4)	0 (0)	**0.046**
≥ 1 positive patch test result, % (n)	48.3 (70)	49.2 (31)	47.6 (39)	0.868
≥ 2 positive patch test result, % (n)	20.0 (29)	17.5 (11)	21.2 (18)	0.537
≥ 3 positive patch test result, % (n)	11.7 (17)	7.9 (5)	14.6 (12)	0.299

P-value is result of differences between patients with and without atopic dermatitis groups. Statistically significant values were marked bold.

Major location of suspected ACD

Regarding the affection of suspected ACD body areas (**table I**), the face corresponded to the main suspected body area in both groups. Particularly, the body area corresponding to the hands was more representative in the group of patients with AD; AD group 17.5% (n = 11) *vs* non-AD group 36.6% (n = 30), p < 0.001. Suspicion of ACD associated with the periumbilical location has only been described in patients with AD; AD group 6.3% (n = 4) *versus* non-AD group 0.0% (n = 0), p < 0.046.

Patch-testing results

The presence of allergic sensitization was similar in both groups. At least the presence of one allergic sensitization was demonstrated in 48.3% (n = 70), corresponding to 49.2% (n = 31) to AD patients (**table I**).

In **table II** the allergens tested and their sensitization prevalence rates for the total sample, AD patients group and non-AD patients group are shown. In **table III** the 20 most common sensitization prevalence rates for each group are listed. The most prevalent allergen for both groups was nickel sulfate. Between the two groups evaluated, there were variable prevalences among the different allergens tested.

In the AD group there was a higher prevalence of sensitization to quaternium 15, parthenolide, diazolidinyl urea, 2-hydroxyethyl methacrylate, hidroperoxide of limonene, compositae mix II, 1,2-dibromo-2,4-dicyanobutane, caine mix II, sesquiterpene lactone mix, and epoxy resin, sensitizations that were not prevalent in the non-AD group. In AD group, none of the most prevalent allergens were included in cosmetic series.

In contrast, allergens such as hydroperoxide linalool, methylchloroisothiazolinone/methylisothiazolinone, fragance mix I, amerchol l-101, disperse orange 3, p-phenylenediamine, imidazolidinyl urea, formaldehyde, and n-isopropyl-n′-phenyl-phenylenediamine had a similarly high prevalence in both analyzed groups.

Table II *- Overview of all routinely tested allergens (European baseline series and cosmetic series), and distribution of positive patch test reactions in the total pediatric population and in with and without atopic dermatitis.*

Allergen	Total (n = 145)	With atopic dermatitis (n = 63)		Without atopic dermatitis (n = 82)		P-value
	% (n positive/n tested)	% (n positive/n tested)	% PRPP	% (n positive/n tested)	% PRPP	
Baseline series						
Nickel sulfate 5% pet	16.0 (23/144)	16.1 (10/62)	70	15.9 (13/82)	62	> 0.99
MCI/MI 0.02% aq	8.3 (12/144)	6.5 (4/62)	100	9.8 (8/82)	88	0.578
Hydroperoxide linalool 1/0.5% pet	6.8 (3/44)	7.4 (2/27)	50	5.6 (1/18)	100	> 0.99
Methylisothiazolinone 0.2% aq	6.3 (9/144)	1.6 (1/63)	100	9.9 (8/81)	88	**0.046**
Amerchol L-101 50% pet	4.9 (7/143)	4.8 (3/62)	67	4.9 (4/81)	25	> 0.99
Cobalt chloride 1% pet	4.9 (7/142)	0.1 (4/62)	50	3.8 (3/80)	33	0.699
Benzisotiazolinona 0.1% pet	4.9 (2/41)	0 (0/21)	NA	10.0 (2/20)	100	0.232
Fragance mix I 8% pet	4.8 (7/145)	4.8 (3/63)	100	4.9 (4/82)	75	> 0.99
Caine mix III 10% pet	4.3 (6/141)	0 (0/60)	0	7.4 (6/81)	17	**0.038**
p-Phenylenediamine 1% pet	4.3 (6/140)	3.3 (2/61)	100	5.1 (4/79)	100	0.697
Disperse Orange 3 1% pet	3.8 (4/106)	4.8 (2/42)	50	3.1 (2/64)	0	0.648
Formaldehyde 2% aq	3.5 (5/143)	3.2 (2/62)	50	3.7 (3/81)	67	> 0.99
Parthenolide 0.1% pet	3.4 (1/29)	6.3 (1/16)	100	0 (0/13)	NA	> 0.99
Diazolidinyl urea 2% pet	2.8 (4/144)	4.8 (3/63)	100	1.2 (1/81)	100	0.319
Quaternium 15 1% pet	2.8 (4/141)	6.7 (4/60)	100	0 (0/81)	NA	**0.031**
Sodium disulfite 1% pet	2.8 (1/36)	0 (0/18)	NA	5.6 (1/18)	0	> 0.99
N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	2.2 (3/138)	1.7 (1/59)	100	2.5 (2/79)	0	> 0.99
Hidroperoxide of limonene 0.2/0.3% pet	2.2 (1/46)	3.7 (1/27)	100	0 (0/19)	NA	> 0.99
Lanolin alcohols 30% pet	2.1 (3/144)	1.6 (1/63)	0	2.5 (2/81)	50	> 0.99
Fragance mix II 14% pet	2.1 (3/144)	0 (0/63)	NA	3.7 (3/81)	67	0.257
Imidazolidinyl urea 2% pet	2.1 (3/141)	3.3 (2/61)	100	1.3 (1/80)	100	0.578
2-Hydroxyethyl methacrylate 1% pet	2.0 (1/49)	4.2 (1/24)	100	0 (0/25)	NA	0.49
Peru balsam 25% pet	1.4 (2/143)	1.6 (1/62)	0	1.2 (1/81)	100	> 0.99
Compositae mix II 2.5% pet	1.1 (1/87)	2.6 (1/38)	100	0 (0/49)		0.437
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (lyral) 5% pet	1.0 (1/98)	0 (0/47)	NA	1.9 (1/51)	100	> 0.99
Propolis 10% pet	0.9 (1/109)	0 (0/46)	NA	1.6 (1/63)	100	> 0.99
1,2-Dibromo-2,4-dicyanobutane 0.3% pet	0.8 (1/129)	1.8 (1/55)	100	0 (0/74)	NA	0.426
Caine mix II 10% pet	0.8 (1/128)	1.8 (1/55)	100	0 (0/73)	NA	0.43
Parabens 12% pet	0.7 (1/142)	1.6 (1/61)	100	0 (0/81)	NA	0.43
Potassium dichromate 0.5% pet	0.7 (1/142)	1.6 (1/62)	100	0 (0/80)	NA	0.437
Sesquiterpene lactone mix 0.3% pet	0.7 (1/139)	1.7 (1/59)	100	0 (0/80)	NA	0.424
Epoxy resin 1.0% pet	0.7 (1/137)	1.7 (1/59)	0	0 (0/78)	NA	0.431

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Allergen	Total (n = 145)	With atopic dermatitis (n = 63)		Without atopic dermatitis (n = 82)		P-value
	% (n positive/n tested)	% (n positive/n tested)	% PRPP	% (n positive/n tested)	% PRPP	
Mercaptobenzothiazole 2% pet	0 (0/144)	0 (0/62)	NA	0 (0/82)	NA	NA
Thiuram mix 1% pet	0 (0/144)	0 (0/62)	NA	0 (0/82)	NA	NA
Colophonium 20% pet	0 (0/144)	0 (0/62)	NA	0 (0/82)	NA	NA
Neomycin sulfate 20% pet	0 (0/142)	0 (0/60)	NA	0 (0/82)	NA	NA
p-tert-Butylphenol formaldehyde resin 1% pet	0 (0/140)	0 (0/61)	NA	0 (0/79)	NA	NA
Budesonide 0.1% pet	0 (0/140)	0 (0/60)	NA	0 (0/80)	NA	NA
Mercapto mix 2% pet	0 (0/139)	0 (0/60)	NA	0 (0/79)	NA	NA
Tixocortol-21-pivalate 1% pet	0 (0/137)	0 (0/59)	NA	0 (0/78)	NA	NA
Disperse blue 106 1% pet	0 (0/137)	0 (0/59)	NA	0 (0/78)	NA	NA
Panthenol 5% pet	0 (0/131)	0 (0/57)	NA	0 (0/74)	NA	NA
Hydrocortisone-17-butyrate 0.1% pet	0 (0/110)	0 (0/43)	NA	0 (0/67)	NA	NA
Primin 0.01% pet	0 (0/97)	0 (0/38)	NA	0 (0/59)	NA	NA
Carba mix 3% pet	0 (0/95)	0 (0/45)	NA	0 (0/50)	NA	NA
Farnesol 5% pet	0 (0/91)	0 (0/36)	NA	0 (0/55)	NA	NA
Clioquinol 5% pet	0 (0/90)	0 (0/36)	NA	0 (0/54)	NA	NA
Textile dye mix 6.6% pet	0 (0/49)	0 (0/24)	NA	0 (0/25)	NA	NA
DMDM hydantoin 1% pet	0 (0/47)	0 (0/25)	NA	0 (0/22)	NA	NA
Lidocaine 15% pet	0 (0/45)	0 (0/22)	NA	0 (0/23)	NA	NA
Cosmetic series*						
Cocamidopropyl betaine 1% aq	2.3 (1/44)	0 (0/21)	NA	4.3 (1/23)	100	> 0.99
Octyl gallate 0.25% pet	2.1 (1/47)	0 (0/22)	NA	4.0 (1/25)	100	> 0.99
Phenoxyethanol 1% pet	2.0 (1/49)	0 (0/23)	NA	3.8 (1/26)	100	> 0.99
Cetearyl alcohol 20% pet	1.9 (1/52)	0 (0/24)	NA	3.6 (1/28)	100	> 0.99
Triethanolamine 2.5% pet	0 (0/56)	0 (0/25)	NA	0 (0/31)	NA	NA
Ethylenediaminetetraacetic acid 1% pet	0 (0/55)	0 (0/24)	NA	0 (0/31)	NA	NA
Chlorocresol 1% pet	0 (0/54)	0 (0/24)	NA	0 (0/30)	NA	NA
Oxybenzone 10% pet	0 (0/52)	0 (0/23)	NA	0 (0/29)	NA	NA
Sorbic acid 2% pet	0 (0/51)	0 (0/24)	NA	0 (0/27)	NA	NA
Chloroxylenol 1% pet	0 (0/50)	0 (0/23)	NA	0 (0/27)	NA	NA
Hexahydro-1,3,5-tris-(2-hydroxyethyl) triazine (Grotan BK) 1% aq	0 (0/49)	0 (0/23)	NA	0 (0/26)	NA	NA
Chloroacetamide 0.2% pet	0 (0/49)	0 (0/23)	NA	0 (0/26)	NA	NA
Propylene glycol 5% pet	0 (0/48)	0 (0/23)	NA	0 (0/25)	NA	NA
Butyl hydroxy toluene 2% pet	0 (0/47)	0 (0/22)	NA	0 (0/25)	NA	NA
Triclosan 2% pet	0 (0/47)	0 (0/21)	NA	0 (0/26)	NA	NA
Abietic acid 10% pet	0 (0/46)	0 (0/22)	NA	0 (0/24)	NA	NA
Butylhidroxianisole 2% pet	0 (0/43)	0 (0/20)	NA	0 (0/23)	NA	NA

Numbers in parentheses represent the number of times that a positive reaction was found to allergen, divided by the total number of times that the allergen was tested. PRPP: Present Relevant per positives; MCI/MI: methylchloroisothiazolinone/methylisothiazolinone; NA: not applicable. P-value is result of differences between patients with and without atopic dermatitis groups. Statistically significant values were marked bold. *Allergens patch tested < 20 times were excluded to avoid non-inferential results (excluded ones are presented in supplementary information).

Table III - *Top 20 most common sensitization prevalence rates for allergens from European baseline series and cosmetic series.*

Top 20 Total	Top 20 with atopic dermatitis	Top 20 without atopic dermatitis
Nickel sulfate 5% pet	Nickel sulfate 5% pet	Nickel sulfate 5% pet
MCI/MI 0.02% aq	Hydroperoxide linalool 1/0.5% pet	**Benzisotiazolinona 0.1% pet**
Hydroperoxide linalool 1/0.5% pet	**Quaternium 15 1% pet**	**Methylisothiazolinone 0.2% aq**
Methylisothiazolinone 0.2% aq	MCI/MI 0.02% aq	MCI/MI 0.02% aq
Amerchol L-101 50% pet	**Parthenolide 0.1% pet**	**Caine mix III 10% pet**
Cobalt chloride 1% pet	Fragance mix I 8% pet	Hydroperoxide linalool 1/0.5% pet
Benzisotiazolinona 0.1% pet	**Diazolidinyl urea 2% pet**	**Sodium disulfite 1% pet**
Fragance mix I 8% pet	Amerchol L-101 50% pet	p-Phenylenediamine 1% pet
Caine mix III 10% pet	Disperse Orange 3 1% pet	Fragance mix I 8% pet
p-Phenylenediamine 1% pet	**2-Hydroxyethyl methacrylate 1% pet**	Amerchol L-101 50% pet
Disperse Orange 3 1% pet	**Hidroperoxide of limonene 0.2/0.3% pet**	**Cocamidopropyl betaine 1% aq***
Formaldehyde 2% aq	p-Phenylenediamine 1% pet	**Octyl gallate 0.25% pet***
Parthenolide 0.1% pet	**Imidazolidinyl urea 2% pet**	**Cobalt chloride 1% pet**
Diazolidinyl urea 2% pet	Formaldehyde 2% aq	**Phenoxyethanol 1% pet***
Quaternium 15 1% pet	**Compositae mix II 2.5% pet**	Formaldehyde 2% aq
Sodium disulfite 1% pet	**1,2-Dibromo-2,4-dicyanobutane 0.3% pet**	**Fragance mix II 14% pet**
Cocamidopropyl betaine 1% aq*	**Caine mix II 10% pet**	**Cetearyl alcohol 20% pet***
N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	Disperse Orange 3 1% pet
Hidroperoxide of limonene 0.2/0.3% pet	**Sesquiterpene lactone mix 0.3% pet**	**Lanolin alcohols 30% pet**
Lanolin alcohols 30% pet	**Epoxy resin 1.0% pet**	N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet

Allergens are shown from most to least frequent. Different top 20 allergens between with and without atopic dermatitis groups were marked bold. *Allergens from Cosmetic series. MCI/MI: methylchloroisothiazolinone/methylisothiazolinone.

Considering the clinical relevance, based on the criteria mentioned above, **table IV** shows the 20 main relevant allergens for each group separately. The most prevalent allergen, nickel sulfate, was considered among the 20 most relevant tested allergens however, it assumed a minor position due to its high prevalence.
The tested allergens methylchloroisothiazolinone/methylisothiazolinone, fragrance mix I, diazolidinyl urea, p-Phenylenediamine, imidazolidinyl urea, methylisothiazolinone, nickel sulfate, and hydroperoxide linalool proved to be relevant in both groups studied. In the AD group, the tested allergens quaternium 15, parthenolide, 2-Hydroxyethyl methacrylate, hydroperoxide of limonene, compositae mix II, 1,2-Dibromo-2,4-dicyanobutane, caine mix II, N-Isopropyl-N′-phenyl-phenylenediamine, sesquiterpene lactone mix, potassium dichromate, parabens, and amerchol L-101 differ from the non-AD group. Based on the results presented, **figure 1** shows the new proposed baseline series for AD patients with a recommendation for ACD evaluation.

Discussion

In this study, we report the experience of our hospital in patch test evaluation in the pediatric population. In our study, most patch-tested patients were aged between 10 and 15 years old. The AD group included significantly younger patients, with most patients aged between 9 and 14 years old. These findings support the notion that ACD increases with age in general and that ACD affects AD patients at an earlier age. They are in line with the probability that AD patients, whose disease presentation appears at a younger age, may have an increased risk of ACD (1, 3). However, the percentage of positive tests in different age groups was similar. In addition, although the safety of patch testing has been verified in children from 6 months of age, the reduced number of children tested at ages below 6 years may reflect the lack of knowledge of the safety profile in this age group (10). Therefore, it is important to the awareness of health professionals for early recognition of this clinical presentation.

Figure 1 *- Purpose for the adapted baseline series for children with AD, with suspected ACD, difficult-to-control AD, new-onset dermatitis and prior to initiating systemic therapy for AD, or when no specific exposure is identified.*

ADAPTED SERIES FOR CHILDREN WITH ATOPIC DERMATITIS WITH RECOMMENDATION TO ACD EVALUATION		
Allergens	**48 h**	**72-96h**
1. Quaternium 15 1% pet		
2. MCI/MI 0.02% aq		
3. Parthenolide 0.1% pet		
4. Fragance mix I 8% pet		
5. Diazolidinyl urea 2% pet		
6. 2-Hydroxyethyl methacrylate 1% pet		
7. Hidroperoxide of limonene 0.2/0.3% pet		
8. p-Phenylenediamine 1% pet		
9. Imidazolidinyl urea 2% pet		
10. Compositae mix II 2.5% pet		
11. 1,2-Dibromo-2,4-dicyanobutane 0.3% pet		
12. Caine mix II 10% pet		
13. N-Isopropyl-N′-phenyl-phenylenediamine 0.1% pet		
14. Sesquiterpene lactone mix 0.3% pet		
15. Methylisothiazolinone 0.2% aq		
16. Potassium dichromate 0.5% pet		
17. Parabens 12% pet		
18. Nickel sulfate 5% pet		
19. Amerchol L-101 50% pet		
20. Hydroperoxide linalool 1/0,5% pet		

Table IV *- Top 20 most common relevant allergens from European baseline series and cosmetic series. Allergens are shown from most frequently relevant in number to least frequent.*

Top 20 with atopic dermatitis	Top 20 without atopic dermatitis
Quaternium 15 1% pet	**Benzisotiazolinona 0.1% pet**
MCI/MI 0.02% aq	Hydroperoxide linalool 1/0.5% pet
Parthenolide 0.1% pet	p-Phenylenediamine 1% pet
Fragance mix I 8% pet	**Cocamidopropyl betaine 1% aq***
Diazolidinyl urea 2% pet	**Octyl gallate 0.25% pet***
2-Hydroxyethyl methacrylate 1% pet	**Phenoxyethanol 1% pet***
Hidroperoxide of limonene 0.2/0.3% pet	**Cetearyl alcohol 20% pet***
p-Phenylenediamine 1% pet	**Hydroxyisohexyl 3-cyclohexene carboxaldehyde (lyral) 5% pet**
Imidazolidinyl urea 2% pet	**Propolis 10% pet**
Compositae mix II 2.5% pet	Imidazolidinyl urea 2% pet
1,2-Dibromo-2,4-dicyanobutane 0.3% pet	Diazolidinyl urea 2% pet
Caine mix II 10% pet	Peru balsam 25% pet
N-Isopropyl-N′-phenyl-pphenylenediamine 0.1% pet	Methylisothiazolinone 0.2% aq
Sesquiterpene lactone mix 0.3% pet	MCI/MI 0.02% aq
Methylisothiazolinone 0.2% aq	Fragance mix I 8% pet
Potassium dichromate 0.5% pet	**Fragance mix II 14% pet**
Parabens 12% pet	**Formaldehyde 2% aq**
Nickel sulfate 5% pet	Nickel sulfate 5% pet
Amerchol L-101 50% pet	**Lanolin alcohols 30% pet**
Hydroperoxide linalool 1/0.5% pet	**Cobalt chloride 1% pet**

Different top 20 allergens between with and without atopic dermatitis groups were marked bold. *Allergens from Cosmetic series. MCI/MI: methylchloroisothiazolinone/methylisothiazolinone.

Despite the interrelation between AD and ACD is controversial, the failure to identify a culprit allergen can have important consequences for the evolution and management of AD. Some of the most common allergens shown in our sample, such as nickel, cobalt, methylchloroisothiazolinone/methylisothiazolinone, hydroperoxide linalool, fragrances, p-phenylenediamine, quaternium 15 and formaldehyde, have been similarly described in the literature as having a high prevalence (11). Regarding patients with and without atopic dermatitis, contact sensitization rates were similar however, after nickel, main allergens were different, mostly related to preservatives (formaldehyde releasers) and plant extracts (parthenolide) that may be present in topical products used in the management of AD. Pointing out particular allergens, nickel as the most prevalent allergen for both groups, is a known commonly identified allergen in many studies of ACD in children and adolescents, likely attributable to the increased use of jewelry, children's toys, metallic components of children's clothing, electronic equipment, and dental appliances (12). Sensitizations to methylisothiazolinone and cobalt were more prevalent in the non-AD group. Although methylchloroisothiazolinone/methylisothiazolinone was one of the most prevalent in both groups, the individual sensitization to methylisothiazolinone showed to be more frequent in non-AD group, which is described in previous studies as a frequent allergen in ACD of hands and face due to its presence in cosmetic and hygiene products, before its ban in 2017 (13). Regarding the prevalence of sensitization to cobalt, our data diverges from some studies published

(11, 14). For example, in China it was found that sensitization to cobalt was higher in patients with AD and was dependent on geographic exposures, not being necessarily related to the coexistence of sensitization to other metals such as nickel (14).

Our study has some limitations that are considered transversal to the other works presented on this topic, namely the possibility of differences in reading techniques between observers. However, in our work, reading and interpretation of patch test results was perfomed always by the same person, to limit this bias. Another limitation may be the difficulty distinguishing between allergic or irritant reactions. The data collected in this work involved children from the same region and a considerable period of time, which may influence the results. We need to consider the high variability of allergen expression in the environment, changes in European legislation, modifications in components of topical products, and lifestyle habits.

In conclusion, confirmed allergic contact dermatitis was relatively common in our sample. It appeared to increase with age, however, the rates of positive tests were similar between age groups. As expected, there were notable differences in sensitization rates of relevant allergens when compared to other European studies, confirming the geographic sensitization variability and need for pediatric adaptation and custom "baseline series".

Patients with and without atopic dermatitis had similar contact sensitization rates however the main allergens were different. We propose the first Portuguese Pediatric Baseline Series adapted for AD patients, based on only the most common and relevant allergens. Overall, this study provides key information on the relationship between AD and ACD in pediatric patch-tested patients in Portugal. Further studies on a national scale are necessary to validate this new series proposal for the Portuguese pediatric population.

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None.

Contributions

JCC, IAC: conceptualization, project administration, methodology, formal analysis, writing - original draft, writing - review & editing. CL: writing - review & editing. ACC, LR: data collection, resources. MG: data collection, resources, project administration, formal analysis, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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