Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: June 30, 2023

Citation: Kefala K, Ponvert C, 2023. Allergic Contact Dermatitis to Chlorhexidine-Containing Antiseptics in Infants and Children: The Origin of Sensitization and The Role of The Excipients in This Sensitization (A Series of Ten Cases)., Medical Research Archives, [online] 11(6). https://doi.org/10.18103/mra.v11i6.4006

DOI
https://doi.org/10.18103/mra.v11i6.4006

ISSN: 2375-1924

RESEARCH ARTICLE

Allergic Contact Dermatitis to Chlorhexidine-Containing Antiseptics in Infants and Children: The Origin of Sensitization and The Role of The Excipients in This Sensitization (A Series of Ten Cases).

Dr Kalomoira Kefala, MD, M.Sc.*
CSMD Clavel, Foundation « Œuvre de la Croix-Saint-Simon », 75019, & Medical office, 22 Rue Quatre Septembre, 75002, Paris, France

Dr Claude Ponvert, MD, PhD,
Faculty of Medicine, University Paris-Descartes, Service de Pneumo-Allergologie Pédiatrique, Necker-Enfants Malades Hospital, Paris, France

*Corresponding E-mail: kalokefkalo@gmail.com

ABSTRACT
The recent COVID-19 pandemic provoked an outstanding increase of infection-control measures, with chlorhexidine becoming an extensively used antiseptic. Allergic contact dermatitis (ACD) to chlorhexidine is considered as a rare event in children, is often difficult to identify, and its diagnosis is often misdiagnosed as other skin diseases.
Thus, we aimed to explore the sensitization to chlorhexidine-containing antiseptics (CCA) in infants and children to determine the origin of their sensitization and the role of the excipients in their dermatosis.
We performed patch tests (PT) with chlorhexidine digluconate 0.5%, benzalkonium chloride 0.1%, benzyl alcohol 10%, 5% and 1% in ten children (1-16.5-year-old, including six children with a personal history of atopy) with severe contact reactions to chlorhexidine-based antiseptics (Biseptine®) and cosmetics. We also performed PT with sodium benzoate 5% in four of the children. Results were measured according to criteria recommended by the International Contact Dermatitis Research Group (ICDRG). Patch test reactions revealed that most children were sensitized to at least two components of CCA (chlorhexidine, benzyl alcohol and/or benzalkonium chloride).
To explore the origin of the sensitization, we searched for umbilical cord care (UCC) with CCA and the use of cosmetics and drugs containing chlorhexidine and excipients of CCA. Most parents reported prior disinfection of umbilical cord with CCA, but this was not always the case.
Allergic contact dermatosis to chlorhexidine, benzyl alcohol and benzalkonium chloride should be considered in infants and children with severe eczema and concomitant allergies. The regular use of cosmetics and drugs containing chlorhexidine, benzyl alcohol, benzalkonium chloride or sodium benzoate should probably be cautioned or avoided in children with severe eczema or pre-existing allergies.
Early suspicion and allergology exploration of ACD to CCA and their excipients is of paramount importance to help prevent severe allergic reactions to topical antiseptics and numerous cosmetics.

Introduction

Allergic contact dermatitis (ACD) to chlorhexidine-containing antiseptics (CCA) and their excipients is considered as a rare event in children, especially in very young children [1-4]. However, clinical manifestations of ACD to CCA and the pathophysiological mechanisms involved have not been extensively investigated in children. Moreover, the origin of sensitization of the children remains often unknown, and groups at risk have not been identified. Consequently, the gaps in knowledge can facilitate sensitization of children through continuing exposure to possible sensitizing agents. Concomitant multiple sensitizations to excipients of CCA have been reported [5].

Children with allergic contact hypersensitivity to CCA can experience a variety of clinical manifestations, from localized reactions to severe eczema. Chlorhexidine-containing antiseptics and cosmetics containing excipients of CCA have been found to be highly sensitizing [4]. Umbilical cord care (UCC) with CCA has been incriminated in sensitization of these children. However, the role of each of the substances contained in CCA (chlorhexidine, excipients) in ACD to chlorhexidine-containing antiseptics remains to be explored. Moreover, exact ways of prevention of ACD to CCA have not been identified.

In a previous publication[6], we have already identified that ACD to CCA could be related to immediate type reactions (edema) in very young children. Therefore, early identification and prevention of such cases is of paramount importance as fragile young children are concerned. In a subsequent study[7], we identified children suffering ACD to CCA sensitized mainly by using UCC. However, CCA was extensively used for UCC for all neonates. Thus, the fact that children allergic to CCA had UCC with CCA could be a coincidence, as many other children could have UCC without developing allergy to CCA. Consequently, the need to identify the populations at risk and the role of later use of chlorhexidine-containing cosmetics (CCC) emerged imminently.

Moreover, we had to answer to the questions raised by the parents for the need to give appropriate advice for caring for their children and the cosmetics that could be used safely. We were, therefore, confronted with the question of the parents about excipients of CCA and CCC, such as sodium benzoate, and the possibility that this could be an allergen for their children and the need to identify the populations at risk.

Thus, in this case report and series, we aimed to identify the clinical characteristics of infants and children with ACD to CCA and their excipients, the origin of their sensitization, the diagnostic and predictive value of patch tests (PT) with chlorhexidine and components of CCA to early diagnose ACD to these antiseptics. We added PT with sodium benzoate to correctly identify the profile of several of our patients.

Our results help to raise awareness of dermatologists, allergists, paediatricians, and general practitioners about ACD to chlorhexidine and components of CCA, even in very young children. We point out unusual clinical signs of ACD to CCA which are usually misdiagnosed to other diseases.

The investigation of uncommon clinical manifestations and patch testing with chlorhexidine and components of CCA is of paramount importance to increase the early detection of such cases. The exploration of the possible origin of sensitization is essential for the prevention of ACD to chlorhexidine-containing antiseptics in infants and children.

Methods

We performed patch tests (PT) with chlorhexidine digluconate 0.5%, benzalkonium chloride 0.1%, benzyl alcohol 10% (Chemotechnique Diagnostics, Vellinge, Sweden), benzyl alcohol 1% and 5% (Smart Practice Europe GmbH, Graven, Germany) in ten children with severe contact reactions to chlorhexidine-based antiseptics (Biseptine®) and cosmetics. We also performed PT with sodium benzoate 5% (Smart Practice Europe GmbH, Graven, Germany) in four of the children (cases 7-10) and PT with polyethylene glycol 400 (PEG 400) in one patient (case 8). Patch tests were performed with aluminium Finn Chambers (Smart Practice Canada, Calgary, AB) in six of the children (cases 1-6) and with chambers IQ Ultra area 0.68 cm^2 (Chemotechnique Diagnostics, Vellinge, Sweden) in four children (cases 7-10). PT were performed on the upper back of the patients. Occlusion time was 2 days, but parents could remove patch test chambers and read the tests earlier in case of intensively irritating PT reactions. Patch tests were read at day (d) 2, d3, d4 and d6-7 after application. We performed further readings if needed, and we noted the day that the patch tests read as positive would no longer be considered positive. Results were measured according to criteria of the International Contact Dermatitis Research Group (ICDRG) [8-10], and were scored as negative (-), doubtful (faint erythema only), weakly positive (+ : nonvascular erythema, infiltration, possibly papules), strongly positive (++: vesicular erythema, infiltration, papules), extremely positive (+++ : intense erythema and infiltration,

coalescent vesicules, bullae) and irritant (IR : soap or shampoo reaction). We considered all reactions + or higher as positive. We also performed Skin Prick tests (SPT) in all children suffering immediate or semi-delayed type reactions to CCA before performing the PT (lancets ALK were used for the SPT).

To determine the origin of the sensitization, we recorded demographic data of the patients, history of umbilical cord care with CCA (UCCA), with eosin-containing antiseptics (UCC Eos) or with restorative skin cream (UCC restorative), frequent use of local antiseptics or cosmetics (hydrating creams, shampoos) containing chlorhexidine, benzyl alcohol, benzalkonium chloride and sodium benzoate (CC cosmetics), and the duration of their use. We recorded if the use of these antiseptics and/or cosmetics was for personal or professional use. We also recorded the type of reaction and the co-existence of atopic skin or other allergies.

Written informed consent was obtained from the parents of the children for the use of the data in relative publications.

Results (patients and results of allergological tests).

Ten patients were explored for clinical reactions to CCA and/or to CC cosmetics. Patient 1, a 3-year-old boy, suffered facial edema [6], patient 3, a 16-year-old hairdresser apprentice, suffered hand eczema, and patient 6, an 11-year-old boy, suffered localized eczema, all of them after use of a CCA [7]. Patient 3 suffered concomitant allergies to other hairdresser products. Patients 1,3, 6 and 7 did not suffer concomitant respiratory or food allergies or asthma. Patients 1, 4, 5, 7, 8, 9,10 suffered recurrent rhinitis.

Patient 2, a 16-year-old hairdresser apprentice, had mite allergy treated with sublingual immunotherapy. She also suffered severe hand eczema (Figure 1A-D) after use of a CCA. Eczema was initially attributed to latex gloves but persisted after replacement with latex-free gloves [7]. Due to the severity of the eczema and the inefficacy of all skin hydrating creams and corticosteroids, the parents ceased the use of all cosmetics.

Patient 4, a 12-month-old boy, had eczema treated with a CC hydrating cream since infancy and suffered allergies to cow's milk, wheat, and soy milk. However, eczema persisted after remission of his allergies and ameliorated only after eviction of CC cosmetics [7].

Patient 5, a 16-month-old girl, suffered eczema since early infancy, and needed to use recurrently multiple hydrating creams. Both of her parents suffered asthma. She suffered urticaria, recurrent rhinitis for a one-month period and severe eczema after the use of a hydrating cream containing benzyl alcohol. Eczema, urticaria and rhinitis ceased after eviction of CC cosmetics [7].

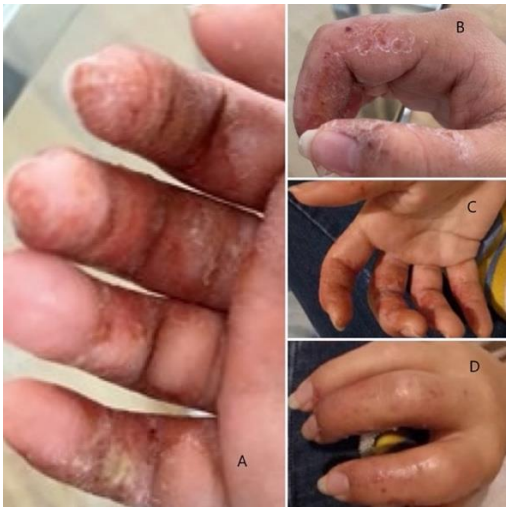

Fig 1A-D. Patient 2 (severe hand contact dermatitis).

Patient 7, a 3-year-old child, suffered edema of the neck and of the eyelids after use of decongestant nasal drops containing benzalkonium chloride and of persistent eczema treated with hydrating creams and an antihistamine drug containing benzyl alcohol. The child suffered recurrent rhinitis, tonsillitis and cough which seemed to aggravate since he went to kindergarten school. The rhinitis and tonsillitis were attributed to viral infections and passive smoking at home. Patch tests were extremely positive for benzalkonium chloride, and strongly positive for sodium benzoate, benzyl alcohol and chlorhexidine. After identification of the allergy to benzalkonium chloride, benzyl alcohol, chlorhexidine, and sodium benzoate, we informed the mother that she should not use drugs and/or cosmetics containing these substances.

Patient 8, a 4-year-old girl, progressively developed eczema, multiple food allergies and severe constipation and was nourished mainly with amino-acid milk formula (AAF). She later developed a respiratory allergy (rhinitis and obstructive sleep apnoea) to *Alternaria Alternata*. Re-initiation of AAF 0-12 months led to resolution of most allergic signs. She used a CC hydrating cream since infancy but suffered difficult healing chickenpox lesions while using a CCA for a long period. This child had not used a CCA for umbilical cord care, but only as a restorative cream. Decongestant drops containing benzalkonium chloride were used to treat her rhinitis but induced mild recurrent nasal bleeding. To treat

her allergies, she had also used an antihistamine containing benzyl alcohol. At age 4 years, eczema was significantly ameliorated after eviction of CC cosmetics, but presented flares. Patch tests were extremely positive for chlorhexidine, strongly positive for benzalkonium chloride, benzyl alcohol 5% and sodium benzoate and weakly positive for benzyl alcohol 1% (Figure 2). She also had an extremely positive patch for PEG 400 (Figure 3), which is a component of the medications used to treat her constipation. Moreover, she had used for many years an hypoallergic shampoo containing sodium benzoate and developed alopecia (Figure 4). She presented a strongly positive patch to sodium benzoate. She started to recover from her hair loss after eviction of this shampoo in parallel with follow-up of AAF (Figure 5).

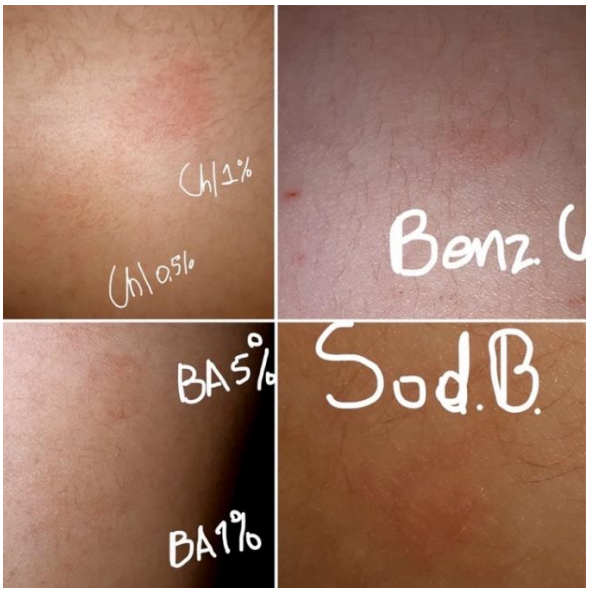

Figure 2. Patient 8: Patch tests for chlorhexidine 1% et 0,5%, Benzalkonium chloride, benzyl alcohol 1% et %, et sodium benzoate.

Figure 3: Patient 8: Patch test for PEG 400.

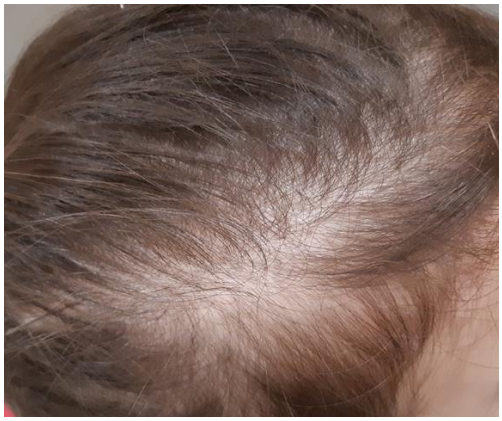

Figure 4. Patient 8: Hair loss.

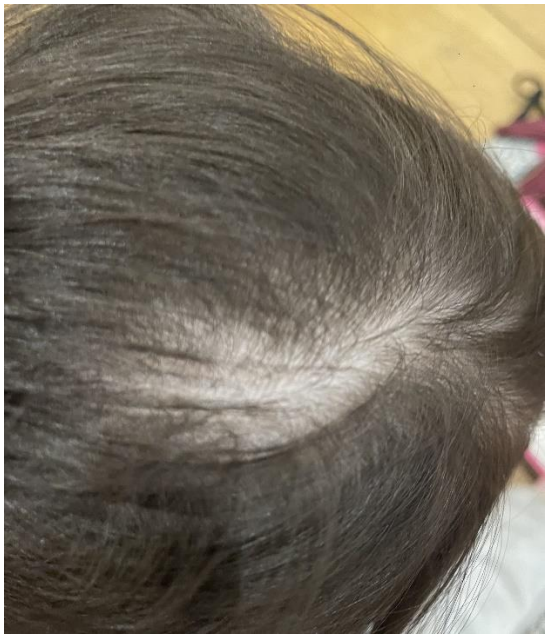

Figure 5. Patient 8: She started to recover from her hair loss.

Patient 9, a 7-year-old boy, and patient 10, a 9 -year-old-boy, were siblings and both suffered severe eczema. Patient 9 also suffered asthma and allergy to mites, whereas patient 10 suffered obstructive sleep apnoea. They also both suffered non-IgE mediated food allergies. Due to recurrent rhinitis, they used decongestant drops containing benzalkonium chloride. Eczema did not ameliorate with recurrent use of hydrating creams and topical corticosteroids. In the two children, patch tests were strongly positive for sodium benzoate and chlorhexidine, and positive for benzalkonium chloride and benzyl alcohol 5%. Eviction of CC cosmetics led to eczema amelioration.

Table 1. Patient's clinical and demographic characteristics, and patch tests results

Patient	Sex (M/F)	Age	Co-existent allergies	Recurrent rhinitis	Reactions	Sensitization	Patch Tests results (scoring according to ICDRG recommendations)					
							Chlorhexidine	Benzalkonium chloride	Benzyl alcohol 1%	Benzyl alcohol 5%	Benzyl alcohol 10%	Sodium Benzoate
1	M	3y	-	+	Facial edema, contact dermatitis	UCCA/repeated antisepsis	+++	+++	++	+++	+++	N/A
2	F	16y	+	+/-	Severe eczema	UCC Eos/ Hairdressing	++	+++	-	+	+	N/A
3	F	16y	-	-	Eczema	UCC Eos /hairdressing	-	+	-	-	-	N/A
4	M	1y	+	+	Eczema	UCCA/repeated cosmetics	+++	+	+	NA	NA	+++
5	F	16 m	+	+	Eczema, urticaria, persistent rhinitis after use of hydrating cream	UCCA/repeated cosmetics	+++	+++	+++	+++	NA	N/A
6	F	11y	-	-	MPR, localized edema	UCC Eos/repeated antisepsis	+++	++	++	++	++	N/A
7	M	3y	-	+	Eczema/recurrent rhinitis/cough/neck and eyelid oedema after use of decongestant nose drops	UCCA/repeated use of decongestant nasal drops/repeated cosmetics	++	+++	++	++	N/A	++
8	F	4y	+	+	Severe eczema/No cicatrisation of chickenpox lesions with CCA, obstructive sleep apnoea, recurrent rhinitis/cough/ decongestant nasal drops	UCC restorative/Antisepsis for chickenpox, use of CC cosmetics, per os antihistamines (benzyl alcohol as excipient)/	+++	++	+	++	N/A	++
9	M	7y	+	+	Severe eczema treated with corticosteroids/ Asthma	UCCA/repeated cosmetics/ decongestant nasal drops	+++	+	-	+	N/A	+++
10	M	9y	+	+	Severe eczema treated with corticosteroids, severe rhinitis, obstructive sleep apnoea	UCCA/repeated cosmetics/ decongestant nasal drops	+++	+	-	+	N/A	+++

Abbreviations: F (female), M (male), y (years), m (months) NA (not applicable), UCCA (umbilical cord care with CCA), UCC Eos (umbilical cord care with eosin-containing antiseptic), UCC restorative (umbilical cord care with restorative skin cream) MPR (maculopapular rash) Chlorhexidine containing cosmetics (CC cosmetics) N/A: non-applicable

Altogether, skin tests were positive for chlorhexidine and benzyl alcohol. in numerous patients. Sensitizations to multiple components of CCA (at least two) were frequent (chlorhexidine, n = 5, benzalkonium chloride, n=1, benzyl alcohol, n=4, sodium benzoate, n=1, PEG 400, n=1). Skin test responses were frequently delayed (usually after 24hours) and persisted for 24 hours or more. The origin of sensitizations was related to umbilical cord care with CCA (UCCA) (early sensitization, n = 6), skin care for eczema (n = 7), respiratory allergy (n = 5), food allergy (n = 5), or professional use (hair care learning, n = 2). Finally, time elapsed between first suggestive symptoms and allergological work-up was long (range = 10 months - 6 years).

Discussion

Allergic contact dermatitis to CCA and their excipients is probably a rare event in children, especially in very young children [1-4]. and thus, has rarely been extensively investigated in children. Moreover, the origin of sensitization of the children remains often unknown, and groups at risk have not been identified. Consequently, lack of knowledge can facilitate sensitization of children through frequent exposure to possible sensitizing agents. Concomitant multiple sensitizations to excipients of CCA have been reported [5].

The case report and series we report illustrate the importance of patch testing when severe eczema does not ameliorate with topical corticosteroids and emollients. The severity of the patch tests reactions (PTR) and their persistence through many days probably reflect the severity of the eczema.

Through the first case we published (Patient 1) [9], we emphasized the emergency of ACD to chlorhexidine and its excipients and the importance of raising awareness of medical practitioners [17]. We pointed out that lack of early identification of such cases could increase the risk for immediate-type reactions to chlorhexidine and its excipients, as it happened in the case of this 3-year-old child [6]. When investigating the origin of sensitization, we recorded that the child had a prolonged UCC with a CCA. We also identified that he used frequently a chlorhexidine-containing soap for his atopic skin and that PT were also positive for the preservative agent benzyl alcohol added in numerous drugs and cosmetics [11,12].

To explore the first case that we present, we realized that benzyl alcohol is commercialized in 3 strengths for patch testing. Smart Practice commercializes 1% and 5% benzyl alcohol and Destaing (Chemotechnique Diagnostics, Allergeaze) commercializes the 10% concentration. There is no consensus about concentrations to be used for patch testing. Smart Practice offers a 1% benzyl alcohol concentration, based upon the recommendations of the North American Contact Dermatitis Group (NACDG) [13]. However, benzyl alcohol 1% sensitization has been reported to be low [13,14]. Thus, benzyl alcohol 10% was added in the NACDG screening series, due to its increasing use in cosmetic products. Since this recommendation, Smart Practice offers a 5% reagent, to be close to the American Contact Dermatitis Society (ACDS) recommendations. In existing publications, benzyl alcohol 10% has been used [15] following ACDS recommendations [16].

NACDG and ACDS recommendations are mostly based on results of studies performed in adult patients [13,14] or adolescents and children older than 6 years. However, young children could have different threshold of reactivity to patch testing. Concerns about use of benzyl alcohol in cosmetics designed for infants and children have already been expressed in the safety assessment report [17]. Due to the lack of clear recommendation, we initially used concentrations 1% and 5% in children ≤ 4 years, but progressively we only used benzyl alcohol concentrations 1% and, if negative, 5%, as we saw that children (*ie:* patient 3) were positive with these concentrations [7]. Thus, we hoped to avoid the (potential) risk of sensitizing children by using high concentrations of benzyl alcohol if this was not necessary.

Benzylic alcohol is metabolized to benzoic acid and sodium benzoate[18-20] is a salt of benzoic acid [6,19]. Thus, we explored a possible cross- or co-sensitization to these two substances in the children with ACD to CCA. Although sodium benzoate is considered as a weak-sensitizing agent [20], concerns have been expressed about activation processes which could increase the risks of sensitization and cross-reactivity among substances in cosmetics [21]. Allergic contact dermatitis to sodium benzoate chloroacetamide has been reported in adults through professional exposure [22]. Patch tests with sodium benzoate were positive in the cases 4, 8, 9 and 10, who were also positive for chlorhexidine, benzyl alcohol and benzalkonium chloride. Thus, the concomitant sensitization to sodium benzoate in children with ACD to CCA and their excipients seems to argue in favour of the role of cosmetics which could also contain sodium benzoate as the origin of sensitization. More specifically, the patients 4 and 8 used a shampoo with sodium benzoate since infancy and they both suffered positive to strongly positive PTR to sodium benzoate.

It is not always clear through which way happens the sensitization to CCA and their

excipients, and which signs should alert physicians to explore for it. Umbilical cord care with a CCA could have been the cause of sensitization in several of the children. Allergic contact dermatitis to chlorhexidine has been diagnosed in children who had no other co-existing allergies (Patients 1, 3 and 6). Among these children, the 3-year-old boy (Patient 1) presented a severe facial edema due to chlorhexidine use. He had had UCC with a CCA, and he had received daily skin care with a chlorhexidine-containing soap.

However, the sensitization of children who did not receive UCC with a CCA (*i.e.*: Patient 8) points out that the sensitization could also occur later in life by using antiseptics and cosmetics containing chlorhexidine and CCA's excipients. Patient 8 did not used CCA for umbilical cord care but used chlorhexidine-containing hydrating cream and shampoo for many years before using the CCA for treatment of her chickenpox lesions. Healing of the chickenpox lesions with the use of a CCA was difficult, with painful lesions persisting through 3 weeks. The persistence of the lesions was attributed to the severity of chickenpox, and the exploration of ACD to chlorhexidine was delayed until she developed signs of persistent eczema. Thus, her sensitization to chlorhexidine and excipients of CCA certainly results from the frequent use of chlorhexidine-containing skin care products. The difficulty of healing chickenpox lesions using a CCA was misdiagnosed to severity of chickenpox infection.

Studies report that positive PTR to benzyl alcohol, benzalkonium chloride and other preservatives are more likely to be found in patients more than 40-year-old who suffer hand dermatitis [13,14]. However, in our study, we found that positive (even extremely positive) PTR to benzyl alcohol were found in very young children (≤ 12-16 months). Moreover, positive PTR to sodium benzoate were found in children ≤ 4 years. These children suffered concomitant mild-moderate to severe eczema, and some of them had other concomitant allergies. Children with eczema use skin care products more frequently than children who do not have eczema or atopic skin. Thus, they would be more prominent to sensitization to preservatives such as benzyl alcohol and sodium benzoate. Children suffering eczema are also more frequently treated with corticosteroids creams, which may induce skin atrophy [23-25]. Even if the skin thinning is mild and reversible, it could favour sensitization to preservatives contained in numerous other skin care products. Patient 5 suffered severe eczema and persistent rhinitis after the use of a cream containing benzyl alcohol. Persistent rhinitis related to severe eczema could be a sign of semi-delayed reaction to benzyl alcohol. Eczema and rhinitis ceased after the cease of CC cosmetics.

Allergic children also use more frequently oral antihistamines. Benzyl alcohol is an excipient of an oral antihistamine [26] used frequently by many of our patients with positive PTR to benzyl alcohol (patients 4, 5, 7, 8, 9 and 10). All of them had positive (even extremely positive) PTR to benzyl alcohol. Parents of patients 5, 7, 8, 9 and 10 reported that their children did not have a good response to the use of this oral antihistamine.

Although, the number of our patients is small (ten patients), it provides powerful information, as it comes from the real need of the patients suffering severe allergic reactions. Moreover, given the high level of sensitization to the allergens studied, and the very young age of the children identified, similar studies cannot be performed in the general pediatric population. They could be performed only in children already suffering allergic complications and asking to find the origin of their complications. It could probably not be ethical to make studies in children with no relative clinical history. Moreover, in larger retrospective studies, detailed history is usually difficult to obtain and correlation to clinical signs is usually hard to certify. The prospective nature of our case series gives power to our study, as the clinical details were more exact, and we could obtain clinical correlations necessary to reach useful conclusions.

Based on these considerations and, although, in our study, the number of children explored for ACD to CCA and CCC is low, the fact that six of the children (60%) had a personal history of atopy, we suggest that atopy (atopic dermatitis, especially) could be a risk factor for ACD to chlorhexidine and excipients contained in CCA and numerous cosmetics and drugs used in these children.

Finally, immediate hypersensitivity reactions have been described with decongestant nose drops use [27] and with salbutamol nebulizer solution (Ventolin®) containing benzalkonium chloride [28]. Patient 7 presented urticaria and severe rhinitis after the use of decongestant nose drops containing this substance. Avoidance of cosmetics and drugs containing chlorhexidine, benzyl alcohol and benzalkonium chloride led to a resolution of his eczema and he no-longer experienced urticaria.

Conclusions

Increased suspicion of physicians upon the possibility of allergy to CCA and its excipients is essential to early identify and explore these cases. An allergy exploration should be performed as soon as possible when chlorhexidine use does not

improve skin symptoms and/or induces allergic-like reactions.

The sensitization could happen using a CCA for UCC. It could also happen later in life through the use of cosmetics and drugs containing chlorhexidine and excipients of CCA.

ACD to chlorhexidine-containing antiseptics and its excipients can be diagnosed in children with co-existing and no co-existing allergies. It could be advised to give special attention to children already suffering eczema and/or co-existing allergies. It could be helpful to consider infants and children with eczema or concomitant allergies as a group at risk for sensitization to CCA, skin care products and drugs' preservatives. Therefore, a special attention should be given before prescription of skin care products and drugs containing chlorhexidine and preservatives in infants and children with atopic skin, eczema and/or concomitant allergies.

Conflicts of Interest Statement

No conflict of interest to declare.

Funding Statement

No funding received for this research.

Acknowledgements

Special acknowledgments to the patients who participated in this research and to their parents.

References

1. Opstrup MS, Johansen JD, Zachariae C, Garvey LH. Contact allergy to chlorhexidine in a tertiary dermatology clinic in Denmark. *Contact Dermatitis*. Jan 2016;74(1):29-36. doi:10.1111/cod.12487
2. Darrigade AS, Leaute-Labreze C, Boralevi F, Taieb A, Milpied B. Allergic contact reaction to antiseptics in very young children. *J Eur Acad Dermatol Venereol*. Dec 2018;32(12):2284-2287. doi:10.1111/jdv.15140
3. Magdaleno-Tapial J, Martinez-Domenech A, Valenzuela-Onate C, Ferrer-Guillen B, Esteve-Martinez A, Zaragoza-Ninet V. Allergic contact dermatitis to chlorhexidine in pediatric patients. *Pediatr Dermatol*. Jul 2019;36(4):540-541. doi:10.1111/pde.13808
4. Galadari A, Darrigade AS, Boralevi F, Milpied B. A child polysensitized to all constituents of Biseptine. *Contact Dermatitis*. Jan 2020;82(1):65-66. doi:10.1111/cod.13393
5. Beaumont C, Darrigade AS, Barbaud A, et al. Multiple cases of sensitization to an antiseptic containing chlorhexidine digluconate/ benzalkonium chloride/benzyl alcohol with different profiles of sensitization in adults and children. *Contact Dermatitis*. Jul 2022;87(1):62-70. doi:10.1111/cod.14085
6. Kefala K, Ponvert C. Un cas pédiatrique de dermite de contact allergique à la Biseptine. Case Report. *Rev Fr Allergol*. 2020;60:614-618. doi:10.1016/j.reval.2020.08.003
7. Kefala K, Ponvert C. Allergic contact dermatitis to chlorhexidine-containing antiseptics and their excipients in children: A series of six cases. *Pediatr Dermatol*. Jan 2023;40(1):151-153. doi:10.1111/pde.15127
8. Lazzarini R, Duarte I, Ferreira AL. Patch tests. *An Bras Dermatol*. Nov-Dec 2013;88(6):879-88. doi:10.1590/abd1806-4841.20132323
9. Fregert S. Patch Testing. In: Publishers YBM, ed. *Manual of Contact Dermatitis*. Munksgaard; 1981:71-81:chap 10.
10. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis*. Oct 2015;73(4):195-221. doi:10.1111/cod.12432
11. Deza G, Gimenez-Arnau AM. Allergic contact dermatitis in preservatives: current standing and future options. *Curr Opin Allergy Clin Immunol*. Aug 2017;17(4):263-268. doi:10.1097/ACI.0000000000000373
12. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther*. 2004;17(3):251-63. doi:10.1111/j.1396-0296.2004.04028.x
13. Atwater AR, Petty AJ, Liu B, et al. Contact dermatitis associated with preservatives: Retrospective analysis of North American Contact Dermatitis Group data, 1994 through 2016. *J Am Acad Dermatol*. Apr 2021;84(4):965-976. doi:10.1016/j.jaad.2020.07.059
14. Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996-2009. *Br J Dermatol*. Jun 2011;164(6):1316-25. doi:10.1111/j.1365-2133.2011.10253.x
15. Suresh R, Murase JE. The role of expanded series patch testing in identifying causality of residual facial dermatitis following initiation of dupilumab therapy. *JAAD Case Rep*. Oct 2018;4(9):899-904. doi:10.1016/j.jdcr.2018.08.027

16. Schalock PC, Dunnick CA, Nedorost S, et al. American Contact Dermatitis Society Core Allergen Series: 2020 Update. *Dermatitis*. Sep-Oct 2020;31(5):279-282. doi:10.1097/DER.0000000000000621
17. Nair B. Final report on the safety assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. *Int J Toxicol*. 2001;20 Suppl 3:23-50. doi:10.1080/10915810152630729
18. Nair B. Final report on the safety assessment of Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water. *Int J Toxicol*. 2001;20 Suppl 3:61-73.
19. Chen H, Zhong Q. Antibacterial activity of acidified sodium benzoate against Escherichia coli O157:H7, Salmonella enterica, and Listeria monocytogenes in tryptic soy broth and on cherry tomatoes. *Int J Food Microbiol*. Jun 2 2018;274:38-44. doi:10.1016/j.ijfoodmicro.2018.03.017
20. Reynolds J, Gilmour N, Baltazar MT, Reynolds G, Windebank S, Maxwell G. Decision making in next generation risk assessment for skin allergy: Using historical clinical experience to benchmark risk. *Regul Toxicol Pharmacol*. Oct 2022;134:105219. doi:10.1016/j.yrtph.2022.105219
21. Safety SCoC. OPINION on Fragrance allergens in cosmetic products. SCCS/1459/11. European Commission; 2012. 27 June 2012. doi:10.2772/77628 https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf
22. Sutton T, Nixon R. Allergic contact dermatitis to sodium benzoate chloroacetamide in a sorbolene lotion. *Australas J Dermatol*. Aug 2006;47(3):209-10. doi:10.1111/j.1440-0960.2006.00276.x
23. Lax SJ, Harvey J, Axon E, et al. Strategies for using topical corticosteroids in children and adults with eczema. *Cochrane Database Syst Rev*. Mar 11 2022;3(3):CD013356. doi:10.1002/14651858.CD013356.pub2
24. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child*. Apr 2016;101(4):365-70. doi:10.1136/archdischild-2015-309522
25. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. Apr 12 2017;357:j1415. doi:10.1136/bmj.j1415
26. Agency EM. Aerius, INN-desloratadine Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/aerius-epar-product-information_en.pdf
27. Mezger E, Wendler O, Mayr S, Bozzato A. Anaphylactic reaction following administration of nose drops containing benzalkonium chloride. *Head Face Med*. Oct 18 2012;8:29. doi:10.1186/1746-160X-8-29
28. Kim SH, Ahn Y. Anaphylaxis caused by benzalkonium in a nebulizer solution. *J Korean Med Sci*. Apr 2004;19(2):289-90. doi:10.3346/jkms.2004.19.2.289