

Contact allergy to chlorhexidine in a tertiary dermatology clinic in Denmark

Morten S. Opstrup, Jeanne D. Johansen, Claus Zachariae and Lene H. Garvey

Department of Dermato-Allergology, National Allergy Research Centre and Allergy Clinic, Copenhagen University Hospital Gentofte, 2900 Hellerup, Denmark
doi:10.1111/cod.12487

Summary

Background. Chlorhexidine is a widely used disinfectant in the healthcare setting and in cosmetic products. A high prevalence of chlorhexidine contact allergy was reported in Denmark in the 1980s (2.0–5.4% of patients patch tested). It is unknown whether the prevalence is still high, which products cause the contact allergy, and whether accidental re-exposure occurs in some patients.

Objectives. To estimate the prevalence of chlorhexidine contact allergy in a tertiary dermatology clinic in Denmark; to investigate whether patch testing with both chlorhexidine diacetate and chlorhexidine digluconate is necessary; to investigate how many patients have combined immediate-type allergy and contact allergy; and to identify which products cause chlorhexidine contact allergy, and whether patients are accidentally re-exposed.

Methods. This was a retrospective study including all patients patch tested with chlorhexidine during 2003–2013 at the Department of Dermato-Allergology at Copenhagen University Hospital Gentofte (n = 8497). All patients with a positive patch test reaction to chlorhexidine were sent a questionnaire comprising questions about the cause of the allergy and re-exposure.

Results. Overall, 1.0% (n = 82) of all patients patch tested with chlorhexidine were positive. A decrease in the prevalence was observed over time, most likely because of lowering of the test concentration from 1.0 to 0.5% in 2008. Of the 82 patients, 28 (0.3%) had positive test reactions to both chlorhexidine salts, 43 (0.5%) had a positive test reaction only to chlorhexidine diacetate, and 11 (0.1%) had a positive test reaction to chlorhexidine digluconate. Three patients were both patch test-positive and prick test-positive. A known cause of the allergy was reported by 19 patients (40%) in the questionnaire: the products used in the healthcare setting were mainly reported, but some reported cosmetic products. Accidental re-exposure was reported by 15 patients (32%), of whom 13 reported symptoms.

Conclusions. The prevalence of chlorhexidine contact allergy does not seem to be higher in Denmark than in other European countries. Patch testing with both chlorhexidine diacetate and chlorhexidine digluconate may be beneficial. Testing for immediate-type allergy in patients with a positive patch test reaction to chlorhexidine is recommended. Chlorhexidine-containing products used in the healthcare setting and in cosmetics are potential causes of sensitization and allergy. Re-exposure is common, highlighting the fact that patients and healthcare personnel need to be well informed about possible sources of exposure.

Key words: chlorhexidine; chlorhexidine allergy; chlorhexidine contact allergy; chlorhexidine contact dermatitis; chlorhexidine diacetate; chlorhexidine digluconate; contact allergy; contact dermatitis.

Correspondence: Morten S. Opstrup, National Allergy Research Centre, Copenhagen University Hospital Gentofte, Kildegårds Allé 28, 2820 Gentofte, Denmark.
Tel: +45 38 67 33 59; Fax: +45 38 67 71 18. E-mail: morten.schoerring.opstrup@regionh.dk

Funding: Financial support from Aage Bangs Fond and the Ministry of Environment was received and is gratefully acknowledged.

Conflicts of interest: All authors declare that there are no conflicts of interest.

Accepted for publication 21 September 2015

Chlorhexidine is superior to other disinfectants and has few side-effects (1, 2). It is widely used in the hospital setting to disinfect skin and mucous membranes (3, 4). Outside the hospital setting, chlorhexidine is also widely used, for example by dentists, in cosmetic products as a preservative, and in products sold over the counter in pharmacies (5, 6).

The focus on contact allergy to chlorhexidine has increased within the last decade, and accordingly the number of publications has risen (7). One reason for this is the increased awareness of the 'hidden' use of chlorhexidine in many products, which can result in chlorhexidine not being suspected as an allergen. Most chlorhexidine-allergic patients have dermatitis caused by contact allergy at the skin site of chlorhexidine exposure; it is estimated that contact allergy to chlorhexidine is diagnosed in 0.01–5.4% of all patch tested patients (5, 8–14). The studies with the highest prevalence rates (2.0–5.4%) are from Denmark, and were conducted in the 1980s (10–12). No newer studies concerning the prevalence in Denmark have been performed, and it remains unknown whether the prevalence is still higher than in other European countries. Chlorhexidine can also cause immediate-type allergy leading to severe reactions such as urticaria, anaphylactic shock, or even cardiac arrest (15, 16). A few case reports have described patients with combined immediate-type allergy and contact allergy, but, so far, the proportion of combined allergy is unknown (17–19).

Chlorhexidine can be used as three different salts: chlorhexidine diacetate [molecular weight (MW) 626 g/mol], chlorhexidine digluconate (MW 898 g/mol), and chlorhexidine dihydrochloride (MW 578 g/mol) (20). According to the European Cosmetics Regulation, all three salts are allowed in cosmetic products (21), but it remains unknown why different salts are used in different products. In 2013, we checked for chlorhexidine content in 2251 cosmetic products in Denmark by reading the ingredient label, and found chlorhexidine in 80 of the products (3.6%) (6). Back then, we did not check which salts were used, but, in a retrospective review of the photographs, we found that 42 products contained chlorhexidine digluconate, 33 contained chlorhexidine dihydrochloride, but none contained chlorhexidine diacetate (the salt used could not be identified in five products). In the same year, we identified 42 different products used in hospitals in the Capital Region of Denmark (3). In a retrospective review of these products, we could see that 27 contained chlorhexidine digluconate, six contained chlorhexidine diacetate, and three contained chlorhexidine dihydrochloride (the salt used could not be identified in six products). In our tertiary dermatology clinic at

Copenhagen University Hospital Gentofte, chlorhexidine diacetate and chlorhexidine digluconate are used for patch testing. In contrast, other centres patch test only with one of the salts. In a study from 1991, some patients had a positive test result with one salt and a negative test result with the other salt, but no newer studies have investigated whether testing with more than one salt is indeed necessary (22).

In Danish studies from the 1980s, it was found that contact allergy to chlorhexidine was primarily diagnosed among men with leg eczema or ulcers (10–12), but there are no newer studies from Denmark or other countries characterizing the patients. In a recent study from Finland, two chlorhexidine-containing corticosteroid creams were suggested to be the principal sources of chlorhexidine contact sensitization (5). In Denmark, however, these products are not available, and it is unknown which chlorhexidine-containing products cause sensitization. Despite the widespread use of chlorhexidine, it is also unknown whether patients are aware of possible sources of exposure.

The aims of this study were (i) to determine the prevalence of contact allergy to chlorhexidine in a tertiary dermatology clinic and to characterize the patients, (ii) to investigate whether patch testing with both chlorhexidine diacetate and chlorhexidine digluconate is necessary, (iii) to estimate how many patients have both immediate-type allergy and contact allergy to chlorhexidine, and (iv) to investigate which products cause allergic reactions, and whether patients are aware of possible sources of chlorhexidine exposure and are able to avoid these.

Materials and Methods

Study population

This was a retrospective study of all patients patch tested with chlorhexidine at the Department of Dermato-Allergy at Copenhagen University Hospital Gentofte during an 11-year-period: 1 January 2003 to 31 December 2013 ($n = 8497$). Chlorhexidine diacetate and chlorhexidine digluconate were routinely applied as a supplement to the baseline series for the entire period: from 1 January 2003 to 1 September 2008 in concentrations of 1.0% aq., and from 1 September 2008 to 31 December 2013 in concentrations of 0.5% aq. The chlorhexidine test substances were prepared in the department from 2003 to 1 September 2008; from 1 September 2008 to 15 March 2009, test substances from Chemotechnique were used; from 15 March 2009 until 31 December 2013, chlorhexidine diacetate 0.5% aq. from Chemotechnique (Vellinge, Sweden) and chlorhexidine digluconate 0.5% aq. from Trolab (Barsbüttel,

Germany) were used. Patient data were collected from the clinical database of contact allergy hosted in the department. Information available from the database included age, MOAHLFA index (Male, Occupation, Atopic dermatitis, Leg dermatitis, Hand dermatitis, Facial dermatitis, and Age > 40 years), and patch test results.

Patch testing

Eight-millimetre Finn Chambers® were used, and patch tests were applied to the upper back. The occlusion time was 48 hr, and reading was performed at D2, D3, and D5/D7, in accordance with ICDRG recommendations. Reactions scored as 1+, 2+ and 3+ were interpreted as positive. Irritant reactions and doubtful reactions were interpreted as negative. In cases of retesting, patch test data obtained at the first visit were used in the analysis. In cases of the same patch test severity on more than one reading, the day of the first reading was used in the analysis.

Prick testing

Prick testing with chlorhexidine was undertaken in some patients with a positive patch test reaction to chlorhexidine. The test was performed on the forearm with chlorhexidine digluconate 0.5% aq. The reaction was read after 20 min. Normal saline and histamine 10 mg/ml served as negative and positive controls, respectively. The test was only considered to be valid when the positive control was positive and the negative control was negative. The criterion for positivity was a mean wheal diameter of ≥ 3 mm.

Statistics

The data were processed with SPSS (SPSS™ Statistics, Chicago, IL, USA; IBM PASW Statistics) for Windows™, edition 22.0. The median and interquartile range (IQR) were used to determine the difference in median age for the populations with and without contact allergy to chlorhexidine. The Mann–Whitney *U*-test was applied for analysis of differences in age between the two groups. The chi-square test was applied for analysis of the MOAHLFA index and irritant reactions. The threshold for statistical significance was predefined as a *p*-value of <0.05.

Questionnaire

In the autumn of 2014, a questionnaire was sent to all patients who had shown a positive reaction to chlorhexidine diacetate and/or chlorhexidine digluconate from 1

January 2003 to 31 December 2013. A reminder was sent to those who had not responded after 3 weeks. The questionnaire comprised six questions (Table A1). First, we asked patients whether they were aware of the cause of the allergy and of possible re-exposures after the allergy was diagnosed. Second, we asked whether patients were aware of the use of chlorhexidine in cosmetic products and in the healthcare setting. Third, we asked whether the allergy to chlorhexidine caused limitations in their everyday life.

Results

A total of 8497 contact dermatitis patients (5714 women and 2783 men) patch tested with chlorhexidine diacetate and/or chlorhexidine digluconate during 1 January 2003 to 31 December 2013 were retrospectively included in the study. Overall, 110 patch tests with chlorhexidine diacetate or chlorhexidine digluconate gave positive results in 82 patients (1.0%). The median age was significantly higher in patch test-positive patients than in patch test-negative patients [55 years (IQR 38–65 years) versus 47 years (IQR 34–60 years), *p* = 0.01]. Of the 82 patients with positive patch test reactions, 28 (0.3%) had positive reactions to both chlorhexidine salts, 43 (0.5%) had a positive reaction only to chlorhexidine diacetate, and 11 (0.1%) had a positive reaction only to chlorhexidine digluconate.

The prevalence rates of sensitization to chlorhexidine are shown in Fig. 1. Overall, a decrease in prevalence was observed over time for both chlorhexidine salts. In 2003, 1.7% of patch tests were positive for one or both salts. In contrast, this figure was 0.3% in 2013. From 1 January 2003 to 31 August 2008, when the test concentrations were 1.0%, the overall prevalence was 1.4% (54/3867); from 1 September 2008 to 31 December 2013, when the test concentrations were lowered to 0.5%, the overall prevalence was 0.6% (28/4630).

Of the positive reactions to chlorhexidine diacetate, 55% (39/71) were weakly positive (1+), 42% (30/71) were strongly positive (2+), and 3% (2/71) were extremely positive (3+). Of the positive reactions to chlorhexidine digluconate, 64% (25/39) were weakly positive, 36% (14/39) were strongly positive, and none was extremely positive (Table 1). In total, 16% (18/110) of the patch tests were positive at day 2, 51% (56/110) were positive at day 3, and 33% (36/110) were positive at days 5–7.

There was a significantly higher rate of irritant reactions when testing was performed with 1.0% chlorhexidine diacetate than when it was performed with 1.0% chlorhexidine digluconate [5.1% (*n* = 199) and

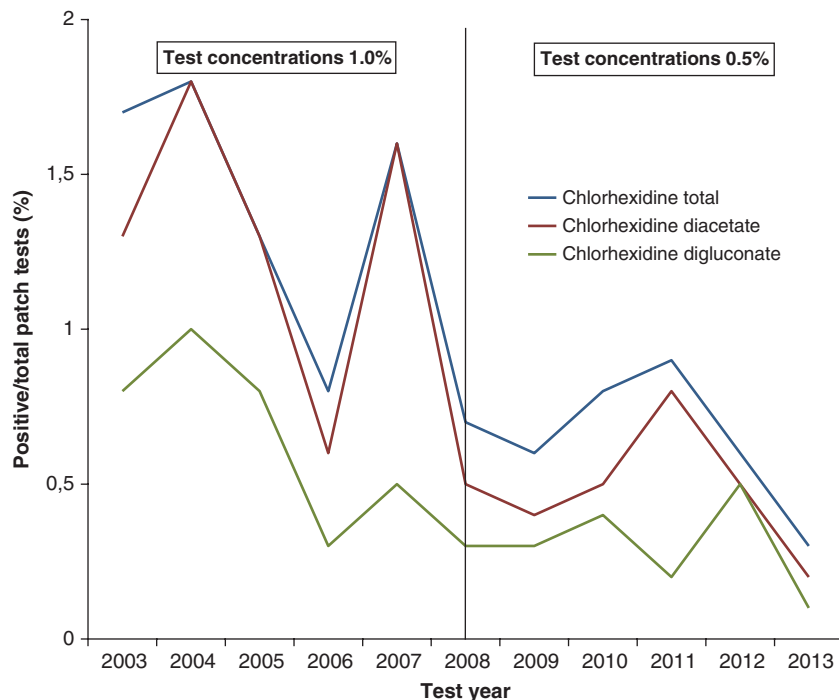


Fig. 1. Prevalence of positive patch test reactions to chlorhexidine 2003–2013.

Table 1. Severity of positive patch test results and year of testing

Test concentration (%)	Year of testing	Chlorhexidine digluconate (n)			Chlorhexidine diacetate (n)		
		1+	2+	3+	1+	2+	3+
1.0	2003	5	1	0	6	4	0
	2004	2	5	0	7	5	1
	2005	3	3	0	7	3	0
	2006	1	1	0	2	2	0
	2007	3	0	0	5	5	0
	1 January to 31 August 2008	1	1	0	2	0	0
	1 September to 31 December 2008	0	0	0	0	1	0
0.5	2009	1	1	0	1	2	0
	2010	2	1	0	2	2	0
	2011	2	0	0	5	1	1
	2012	4	1	0	1	4	0
	2013	1	0	0	1	1	0

2.1% ($n = 80$), respectively, $p < 0.00001$]. In contrast, there was no statistically significance difference in the rate of irritant reactions when testing was performed with 0.5% chlorhexidine diacetate and when it was performed with 0.5% chlorhexidine digluconate [0.5% ($n = 24$) and 0.3% ($n = 15$), respectively, $p = 0.14$]. Overall, there was a significantly higher rate of irritant reactions in the group tested with 1.0% chlorhexidine diacetate and 1.0% chlorhexidine digluconate than in the group tested with 0.5% chlorhexidine diacetate and 0.5% chlorhexidine

Table 2. MOAHLFA index for patients with positive and negative patch tests results for chlorhexidine (a positive reaction to either chlorhexidine diacetate, chlorhexidine digluconate, or both)

Total tested	% (n) positive (n = 82)	% (n) negative (n = 8415)	p-value*
Male sex	58.5 (48)	32.5 (2735)	<0.00001
Occupational	15.9 (13)	19.8 (1664)	0.37
Atopic dermatitis	12.2 (10)	16.8 (1417)	0.26
Hand dermatitis	41.5 (34)	38.7 (3258)	0.61
Leg dermatitis	18.3 (15)	4.7 (392)	<0.00001
Face dermatitis	15.9 (13)	24.1 (2029)	0.08
Age above 40 years	74.4 (61)	66.0 (5554)	0.11

Significant values are in bold.

*Pearson chi-square.

digluconate [3.6% ($n = 279$) and 0.4% ($n = 39$), respectively, $p < 0.00001$].

The findings for the MOAHLFA index are shown in Table 2. Chlorhexidine allergy was significantly associated with male sex and leg dermatitis.

Prick testing

Of the 82 patients with a positive patch test reaction to chlorhexidine, 29 were prick tested with chlorhexidine digluconate, and 3 were positive. Of the 3 patients, 1 had a strongly positive (2+) patch test reaction to 1.0% chlorhexidine digluconate and an extremely positive (3+) digluconate [3.6% ($n = 279$) and 0.4% ($n = 39$), respectively, $p < 0.00001$].

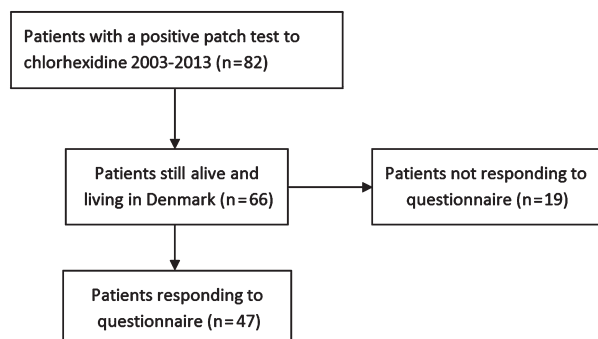


Fig. 2. Flowchart of response to questionnaire.

patch test reaction to 1.0% chlorhexidine diacetate; the 2 remaining patients had strongly positive (2+) patch test reactions to 1.0% and 0.5% chlorhexidine diacetate, respectively.

Questionnaire

Of the 82 patients with a positive patch test reaction to chlorhexidine, 66 were still alive and living in Denmark, and were mailed the questionnaire (see flowchart in Fig. 2). A total of 71% ($n = 47$) responded. Of these, during the initial investigation, 53% ($n = 25$) were positive only for chlorhexidine diacetate, 13% ($n = 6$) were positive only for chlorhexidine digluconate, and 34% ($n = 16$) were positive for both salts. A total of 62% ($n = 29$) had a weakly positive patch test reaction (1+), 36% ($n = 17$) had a strongly positive patch test reaction (2+), and 2% ($n = 1$) had an extremely positive patch test reaction (3+). Overall, 60% ($n = 29$) were tested before 1 September 2008 with concentrations of 1.0%, and 40% ($n = 19$) were tested after 1 September 2008 with a concentration of 0.5%. The MOAHLFA index among those who responded was comparable to that of the whole group of patch test-positive patients [male sex 53% ($n = 25$); occupational 19% ($n = 9$); atopic dermatitis 19% ($n = 9$); hand dermatitis 45% ($n = 21$); leg dermatitis 11% ($n = 5$); face dermatitis 15% ($n = 7$); age > 40 years 74.5% ($n = 35$)].

A total of 19 patients (40%) reported knowing the cause of the allergy (Table 3); of these, 4 reported more than one product as the cause. Mainly healthcare products, but also cosmetic products, were reported as causes. Regarding exposure after the diagnosis was established, 15 patients (32%) reported a known re-exposure; also here, mainly healthcare products but also cosmetic products were reported. Of the 15 patients reporting re-exposure, 13 reported symptoms: most reported a

Table 3. Questionnaire results regarding cause of the allergy and possible re-exposure

	Number (%)	Reported products (n)
Patients reporting a known cause	19 patients (40)	Cream (7); hair product (5); make-up or make-up remover (1); wet wipe or other skin disinfectant (5); mouth wash (2); wound dressing (5); product used at the hospital or by a doctor (6); product used by a dentist (3); other (2)*
Patients reporting re-exposure after the diagnosis was established	15 patients (32) (of these, 13 patients reported symptoms)	Cream (5); hair product (2); wet wipe or other skin disinfectant (7); mouth wash (3); wound dressing (4); product used at the hospital or by a doctor (6); product used by a dentist (3); other (1)*

In total, 22 patients (47%) reported a known cause and/or symptoms at re-exposure (some patients reported both a known cause and symptoms at re-exposure).

*Many reported more than one cause/exposure.

rash and/or skin itching ($n = 12$), but some also reported general discomfort ($n = 4$) or breathlessness ($n = 2$). Concerning the timing between exposure and symptoms, 6 of 13 reported symptoms within an hour, 3 of 13 reported symptoms between 1 and 24 hr after exposure, and 2 of 13 reported symptoms more than 24 hr later (2 did not report the timing). Of the 6 patients reporting symptoms within an hour, 5 were tested with a prick test during the initial investigations, and they were all negative.

Regarding the patients' knowledge about possible exposure to chlorhexidine in cosmetic products and in the healthcare setting, only 38% ($n = 18$) were aware of its use in cosmetics, but 45% ($n = 21$) checked for chlorhexidine in cosmetic products before using them. In contrast to these findings, 83% ($n = 39$) were aware of the use of chlorhexidine in hospitals and by dentists, and the same number of patients reported informing about the allergy when in contact with hospitals or a dentist.

Regarding possible work-related exposure, 15% ($n = 7$) had been in contact with chlorhexidine at work: 1 nurse was exposed from skin swabs and a hand disinfectant; 1 nurse assistant and 1 painter reported exposure, but did not specify from what product; 1 cleaner was exposed from a soap; 1 blacksmith was exposed from a hand cleaner; 1 machine operator was exposed from an ointment; and 1 patient was exposed from different products when working in two different jobs – from a hair product when working as a hairdresser, and from cleaning swabs

when working in a kindergarten. The 2 latter patients had to quit their jobs because of the allergy.

Regarding the burden of disease, 21% ($n = 9$) reported that the allergy caused limitations in their everyday life.

Discussion

In this retrospective study evaluating patients diagnosed with contact allergy to chlorhexidine in a Danish tertiary dermatology clinic, we found that 1.0% of all patients patch tested from 2003 to 2013 had a positive patch test reaction to chlorhexidine. This finding is in line with the prevalence found in studies from other European countries, but is lower than the prevalence in previous studies from Denmark in the 1980s (5, 8–13). Most of the reactions were weakly positive, which is in line with a recent study from Finland, but is in contrast to an older study from our clinic, where most of the reactions were strongly/extremely positive (5, 11). Notably, in our centre, there was a marked decrease in the prevalence, from 1.7% in 2003 to 0.3% in 2013. This is probably because we lowered the test concentration from 1.0 to 0.5% in 2008. Currently, the optimal test concentration remains unknown, and different centres use different concentrations: The European Network for Drug Allergy recently suggested a test concentration of 1% (23), but some centres use 0.5% (5, 9). In this study, we found that 0.5% chlorhexidine diacetate and 0.5% chlorhexidine digluconate caused fewer irritant reactions than 1.0% chlorhexidine diacetate and 1.0% chlorhexidine digluconate. These findings are in line with an older study from our clinic, which also found that, especially, 1.0% chlorhexidine diacetate is a strong irritant (22). Additionally, two older studies found that it was difficult to reproduce the test results when patch testing (10, 12). Taken together, these findings suggest that 1.0% is too high as a test concentration. Nonetheless, no studies have investigated whether testing with 0.5% is reproducible or whether it causes false-negative results. Therefore, future studies should focus on finding the optimal concentration for patch testing with chlorhexidine; such studies could, for instance, include use testing or patch testing with titrated concentrations, and repeated open applications of solutions of chlorhexidine.

In our questionnaire study, 40% of respondents reported a potential cause of their allergy – products used in the healthcare setting were mainly reported, but some reported cosmetic products. The remaining patients (60%) did not report a known cause of their allergy, and there could be several reasons for this. First, a positive patch test reaction to chlorhexidine indicates sensitization, but this may not lead to allergic symptoms

in all patients. Second, some patients may not remember an exposure a long time ago. Third, some patients may have been using a product causing the symptoms without knowing this. Indeed, the last of these could very well be the case in some patients, because 62% of the patients in the questionnaire were unaware of the use of chlorhexidine as a preservative in cosmetic products, and 17% were unaware of the use in the healthcare setting. Exposure assessment is an important part of allergy investigation, but the data saved in the database from the time of the original investigation were incomplete, and could therefore not be included as a supplement in this study.

Notably, 32% of patients reported re-exposure to chlorhexidine after the diagnosis was established, and almost all reported symptoms. This highlights how difficult it is to avoid chlorhexidine, and how important it is to give information about possible exposure routes when a patient is diagnosed with chlorhexidine allergy.

In our clinic, patch testing is performed with both chlorhexidine diacetate and chlorhexidine digluconate. Although chlorhexidine digluconate is more frequently used in both the healthcare setting and in cosmetic products in Denmark, more than half of the patients were positive only for chlorhexidine diacetate. Therefore, this salt is especially important when testing for chlorhexidine contact allergy is performed. Nonetheless, some patients were positive only for chlorhexidine digluconate, and testing should therefore include both salts. Chlorhexidine dihydrochloride is widely used in Denmark, mainly in cosmetic products, but it is not included in diagnostic testing in our centre, or, to our knowledge, in any other centres. Future studies should investigate the possibility of chlorhexidine dihydrochloride causing contact sensitization/allergy.

In this study, 3 patients with a positive patch test reaction to chlorhexidine were also prick test-positive for chlorhexidine digluconate, indicating combined immediate-type allergy and contact allergy. Therefore, we recommend testing for immediate-type allergy in patients with a positive patch test reaction to chlorhexidine. Investigations should include prick testing with chlorhexidine digluconate 0.5% and measurement of specific IgE (23, 24). A limitation of this study is that measurement of specific IgE was not performed, but this is now included in our routine testing for immediate-type allergy. In immediate-type chlorhexidine allergy, testing only with chlorhexidine digluconate is recommended (23). As found in this study, many of the patients with a positive patch test reaction to chlorhexidine were positive only for chlorhexidine diacetate. Therefore, the

role of this salt should be further investigated in the group of patients suspected of having immediate-type chlorhexidine allergy.

Three characteristics separated the group of patients with a positive patch test reaction to chlorhexidine from the group with negative patch test results for chlorhexidine: higher age, male sex, and leg eczema. These characteristics are in line with findings in Danish studies from the 1980s (10–12). At that point, dressings containing chlorhexidine diacetate 0.5% were believed to be the cause of the contact allergy. Today, the same dressings are still used in Denmark (3), and 5 of the 47 patients in the questionnaire reported exposure to chlorhexidine in dressings. Therefore, it seems that chlorhexidine-containing dressings can sensitize some patients. However, 4 of the 5 patients also reported other exposures in the healthcare setting.

In conclusion, 1.0% of patients tested in our tertiary dermatology clinic had a positive patch test reaction to chlorhexidine in 2003–2013. The prevalence decreased over the 11-year-period, probably because of a lower test concentration (0.5% versus 1.0%) in the second half of the period. Male sex, leg eczema and higher age were more predominant in the patch test-positive group than in the patch test-negative group. It may be beneficial to patch test with both chlorhexidine diacetate and chlorhexidine digluconate, but the optimal test concentration remains to be established. Three patients were both patch test-positive and prick test-positive; we recommend testing for immediate-type allergy in patch test-positive patients. Finally, in most patients, the allergy was caused by chlorhexidine used in the healthcare setting, but, for some, cosmetic products were responsible. Moreover, 32% were re-exposed after the diagnosis, highlighting the fact that patients and healthcare personnel need to be well informed about possible sources of exposure.

Appendix

Table A1. Questionnaire about chlorhexidine contact allergy

1a.	Do you know what product caused your allergy to chlorhexidine?
	Yes; No
1b.	If yes in 1a: What product caused the allergy?
	Cream; hair product; make-up or make-up remover; wet wipe or other skin disinfectant; mouth wash; wound bandage; product used at the hospital or by a doctor; product used by a dentist; other: _____

Table A1. Continued

2a.	Have you been exposed to chlorhexidine since the allergy was diagnosed?
	Yes; No; Don't know
2b.	If yes in 2a: What product was it?
	Cream; hair product; make-up or make-up remover; wet wipe or other skin disinfectant; mouth wash; wound bandage; product used at the hospital or by a doctor; product used by a dentist; other: _____
2c.	If yes in 2a: What symptoms did you experience?
	Rash; itching skin; urticaria; breathing difficulties; feeling unwell; fainting; other: _____
2d.	If yes in 2a: When did you experience the symptoms?
	0–60 min; 1–24 hr; more than 24 hr
3a.	Have you been exposed to chlorhexidine in your current job or in a previous job?
	Yes; No; Don't know
3b.	If yes in question 3a: What was your job?

3c.	If yes in question 3a: What product contained chlorhexidine?

3d.	If yes in question 3a: Did you have to quit your job?
	Yes; No
4a.	Do you know that chlorhexidine can be used in some cosmetic products?
	Yes; No
4b.	Do you check whether there is chlorhexidine in a cosmetic product before you use it?
	Yes; No
5a.	Do you know that chlorhexidine is used at hospitals and by dentists?
	Yes; No
5b.	Do you mention your allergy when you are at a hospital or at your dentist?
	Yes; No
6a.	Does the allergy cause limitations in your everyday life?
	Yes; No
6b.	If yes in 6a: In what way does the allergy limit you?

Translated from Danish.

Acknowledgements

We thank Pao-Lung Tsai, data manager at the National Allergy Research Centre, for valuable help with data extraction.

References

- 1 Lim K-S, Kam P C. Chlorhexidine – pharmacology and clinical applications. *Anaesth Intensive Care* 2008; **36**: 502–512.
- 2 Darouiche R O, Wall M J, Itani K M F et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med* 2010; **362**: 18–26.
- 3 Opstrup M, Johansen J, Garvey L. Chlorhexidine allergy: sources of exposure in the health-care setting. *Br J Anaesth* 2015; **114**: 704–705.
- 4 Odedra K M, Farooque S. Chlorhexidine: an unrecognised cause of anaphylaxis. *Postgrad Med J* 2014; **90**: 709–714.
- 5 Liippo J, Kousa P, Lammintausta K. The relevance of chlorhexidine contact allergy. *Contact Dermatitis* 2011; **64**: 229–234.
- 6 Opstrup M S, Johansen J D, Bossi R, Lundov M D, Garvey L H. Chlorhexidine in cosmetic products – a market survey. *Contact Dermatitis* 2015; **72**: 55–58.
- 7 Silvestri D L, McEnery-Stonelake M. Chlorhexidine: uses and adverse reactions. *Dermatitis* 2013; **24**: 112–118.
- 8 Hasan T, Rantanen T, Alanko K et al. Patch test reactions to cosmetic allergens in 1995–1997 and 2000–2002 in Finland – a multicentre study. *Contact Dermatitis* 2005; **53**: 40–45.
- 9 Dastychová E, Necas M, Vasku V. Contact hypersensitivity to selected excipients of dermatological topical preparations and cosmetics in patients with chronic eczema. *Acta Dermatovenol Alp Panonica Adriat* 2008; **17**: 61–68.
- 10 Bechgaard E, Ploug E, Hjorth N. Contact sensitivity to chlorhexidine? *Contact Dermatitis* 1985; **13**: 53–55.
- 11 Osmundsen P. Contact dermatitis to chlorhexidine. *Contact Dermatitis* 1982; **8**: 81–83.
- 12 Lasthein Andersen B, Brandrup F. Contact dermatitis from chlorhexidine. *Contact Dermatitis* 1985; **13**: 307–309.
- 13 Perrenoud D, Bircher A, Hunziker T et al. Frequency of sensitization to 13 common preservatives in Switzerland. *Contact Dermatitis* 1994; **30**: 276–279.
- 14 Goon A T, White I R, Rycroft R J, McFadden J P. Allergic contact dermatitis from chlorhexidine. *Dermatitis* 2004; **15**: 45–47.
- 15 Garvey L H, Kroigaard M, Poulsen L K, Skov P S, Mosbech H, Venemalm L, Degerbeck F, Husum B. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–415.
- 16 Nakonechna A, Dore P, Dixon T, Khan S, Deacock S, Holding S, Abuzakouk M. Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom. *Allergol Immunopathol* 2014; **42**: 44–49.
- 17 Lauerma A I. Simultaneous immediate and delayed hypersensitivity to chlorhexidine digluconate. *Contact Dermatitis* 2001; **44**: 59.
- 18 Bergqvist-Karlsson A. Delayed and immediate-type hypersensitivity to chlorhexidine. *Contact Dermatitis* 1988; **18**: 84–88.
- 19 Ebo D G, Stevens W J, Bridts C H, Matthieu L. Contact allergic dermatitis and life-threatening anaphylaxis to chlorhexidine. *J Allergy Clin Immunol* 1998; **101**: 128–129.
- 20 Sigma Aldrich. Product catalogue. Available at: <http://www.sigmaaldrich.com/catalog/search?term=chlorhexidine&interface=All&N=0&mode=match&20partialmax&lang=en®ion=DK&focus=product> (last accessed 15 October 2015).
- 21 European Commission. CosIng. Available at: <http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=28789> (last accessed 15 October 2015).
- 22 Knudsen B, Avnstorp C. Chlorhexidine gluconate and acetate in patch testing. *Contact Dermatitis* 1991; **24**: 45–49.
- 23 Brockow K, Garvey L H, Aberer W et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–712.
- 24 Opstrup M S, Malling H-J, Kroigaard M, Mosbech H, Skov P S, Poulsen L K, Garvey L H. Standardized testing with chlorhexidine in perioperative allergy – a large single-centre evaluation. *Allergy* 2014; **69**: 1390–1396.