

Contact allergy in chronic leg ulcers: results of a multicentre study carried out in 423 patients and proposal for an updated series of patch tests

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Background: There is a lack of prospective studies investigating contact sensitization in patients with chronic leg ulcers.

Objectives: To determine the frequency of contact sensitization in patients with chronic leg ulcers using a special series of patch tests and to determine whether the number of sensitizations was correlated with the duration of the chronic leg ulcers.

Patients/methods: Multicentre study carried out in patients with chronic leg ulcers; patch tests with the European baseline series and with an additional 34 individual allergens or mixes and 3 commercial products.

Results: Of the 423 patients (301 women, 122 men, mean age 68.5 years) with chronic leg ulcers, 308 (73%) had at least one positive patch test with 3.65 positive patch tests per patient. The main allergens were *Myroxylon pereirae* (41%), fragrance mix I (26.5%), antiseptics (20%), and corticosteroids (8%). The number of positive tests per patient was not correlated with the cause of ulcer but was increased with the duration of the ulcer with a statistical difference between the group of the <1 year compared with the group >10 years duration.

Conclusions: From this large prospective multicentre study, polysensitization is frequent in patients with chronic leg ulcers, increasing with the duration of the ulcer. We propose avoidance of topical antiseptics and ointments containing perfumes in patients with chronic leg ulcers and an updated patch test series for investigating these patients.

Key words: antiseptics; chronic leg ulcer; contact allergy; corticosteroids; patch tests; perfume sensitization. © 2009 John Wiley & Sons A/S.

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In a previous single-centre study undertaken with individual allergens, and also a large number of commercial dressings used to treat chronic leg ulcers (1), we demonstrated that 82.5% of 359 patients had at least one positive patch test reaction. We emphasized that most of these patients had a polysensitization. Other smaller series of patients have also showed a high frequency of

contact allergies in such patients (2–5). In a multi-analysis, Machet et al. (6) determined that 72% of 1185 cases published from 1991 to 2003 had a positive patch test. In most of the previous studies, the number of patients reported was low and the specific series used in testing the patients had a limited number of allergens and/or a high number of commercial dressings that led to

difficulties in comparing the results from one centre to another. Of 100 patch-tested patients with chronic leg ulcers, Paramsothy et al. (5) observed that the prevalence of positive patch tests was significantly higher in patients with surrounding eczema and that the duration of the ulcer was longer in patients with positive patch tests than in those with negative patch tests.

The main objective of this study was to determine the frequency of sensitization to substances present in the dressings or topical drugs frequently used for patients suffering from chronic leg ulcers. A large number of patients were tested in a prospective study with a specific series of patch tests, mainly composed of commercial material for patch tests with some commercial ointments or dressings. The secondary objectives were to study the differences in terms of positive tests per patient observed from one area to another with different therapeutic habits and to determine whether the number of sensitizations was correlated or not with the duration of the chronic leg ulcers, the presence of leg eczema, and the type of chronic leg ulcers.

Patients and Methods

A prospective multicentre study was conducted during 58 months including 423 consecutive patients referred, for the first time, to one of the four participating dermatology centres. For each patient, the following information was collected before patch testing: age, sex, duration of the ulcer (classified into three groups: <1 year, 1–10 years, and >10 years), cause of the leg ulcer as diagnosed by clinical and echo-Doppler examinations, and the existence of present eczematous lesions surrounding the ulcer.

All patients were patch tested with a European baseline series and a series designed for leg ulcer patients consisting of 34 individual allergens or 'mixes' from Chemotechnique Diagnostics (Malmö, Sweden) or Hermal Trolab (Reinbeck, Germany), and a few allergens prepared as proposed by De Groot (7) (see Table 1 for list of allergens, vehicles, and concentrations). All patients were also tested with three commercial products:

- (1) Comfeel transparent[®] containing carboxymethylcellulose synthetic adhesive elastomer and elastic polyurethane (Coloplast Laboratory, Rosny-sous-Bois, France).
- (2) Duoderm E[®] containing polyurethane carboxymethylcellulose, pectin, gelatine, and adhesive elastomer polymers (Convatec Laboratory, Rueil-Malmaison, France).

- (3) Biafine[®] ointment containing, ethylene glycol stearate, stearic acid, cetyl palmitate, solid and liquid petrolatum, perhydro-squalene, propylene glycol, avocado oil, triethanolamine, potassium sorbate, methylparaben, propylparaben, aroma, and purified water (Medix Laboratory, Houdan, France).

During the past 3 years of the study, EMLA[®] cream [containing lidocaine, prilocaine, castor oil, carbomer, sodium hydroxide, and purified water (AstraZeneca Laboratory, Rueil-Malmaison, France)] was also tested in all newly included patients (210 patients).

When possible, dressings used by the patients were also tested. Patch tests were performed on the upper back under Finn Chambers[®] on Scanpor tape[®] (Epitest Ltd Oy, Tuusula, Finland), and reactions were read at D2 and D3 or D4 and recorded according to the International Contact Dermatitis Research Group recommendations for patch test reading (8). We only took into account positive reactions ($\geq 1+$) or stronger, that is doubtful reactions with erythema, but no infiltration were not considered as positive results.

Data were processed using 4th dimension software by 4D Inc., San Jose, CA, USA. The data analysis for this paper was generated using STATVIEW version 5 (SAS Institute Inc., Cary NC, USA). Categorical variables were compared among the groups of patients by a chi-squared analysis. For quantitative variables, approximate normal distribution was assessed. Results for continuous variables were expressed as mean $\pm$ standard deviation (SD), and comparisons to investigate the relationship between continuous variables and groups were analysed by the one-way analysis of variance (ANOVA). Correlation between quantitative variables was calculated through Spearman's rank correlation rho test. Significance was set at the $P \leq 0.05$ level for all comparisons, and the Bonferroni correction for multiple comparisons was used when appropriate.

Results

Four hundred and twenty-three patients, 301 women and 122 men (without statistically significant differences between sex ratio from one centre to another), mean age of 74.2 years, were included (239 cases in Nancy, 114 cases in Dijon, and 34 cases in both Ivry and Strasbourg). With a Fisher's test, there was no global statistically significant difference between the mean ages of the patients from Ivry (77.5 years), Nancy (74.6 years), and

Table 1. Results of patch tests with 62 different substances in 423 patients suffering from chronic leg ulcers^a

Test substance	Percentage and vehicle	Number of positive tests	Percentage of sensitized patients (423 patients)	Percentage in a meta-analysis, 1185 patients (1991–2003), Machet et al. (6)
<i>Myroxylon pereirae</i> (Balsam of Peru)	25% pet.	172	40	25.4
<i>Fragrance mix I</i>	8%	112	26.5	18.8
Amerchol L101 [®]	50% pet.	83	19.6	
Lanolin (wool alcohols)	30% pet.	75	17.7	17.5
Povidone–iodine	10% water	54	12.7	
Benzalkonium chloride	0.1% pet.	44	10.4	
Neomycin sulfate	20% pet.	39	9.2	Aminoglycosides: 13.9
Biafine pure [®]	as is	36	8.5	
Colophonium (colophony)	20% pet.	32	7.6	
Budesonide	0.1 pet.	30	7.1	
Cetearyl alcohol (cetostearyl alcohol)	20% pet.	24	5.7	
Nickel sulfate	5%	23	5.4	
Thimerosal	0.1% pet.	23	5.4	
Thiuram mix	1% pet.	18	4.25	5.5
Sorbitan sesquioleate	20% pet.	17	4	
Cetrimide	0.1% water	17	4	
Duoderm E [®]	as is	17	4	
Propylene glycol	10% water	15	3.5	
Paraben mix	16% pet.	13	3.1	
Sodium metabisulfite	1% pet.	13	3.1	
Bufexamac	5% pet.	13	3.1	
Eosin	50% pet.	12	2.8	
Epoxy resin	1% pet.	11	2.6	
Euxyl K400 [®]	0.5% pet.	11	2.6	
(methyl dibromo glutaronitrile and phenoxyethanol)				
Gentamycin	10% water	11	2.6	
Paraphenylenediamine free base	1% pet.	10	2.4	
Octyl gallate	0.3% pet.	10	2.4	
Chlorhexidine digluconate	0.5% water	10	2.4	
Cobalt chloride	1% pet.	8	1.9	
Potassium dichromate	0.5% pet.	7	1.7	
Triethanolamine	2.5%	7	1.7	
Dodecyl gallate (lauryl gallate)	0.5% pet.	7	1.7	
Tixocortol pivalate	1% pet.	7	1.7	
Hydrocortisone 17-butyrate	0.1% pet.	7	1.7	
Chloquinol	5% pet.	6	1.4	
Mercapto mix	2% pet.	6	1.4	
Sesquiterpene lactone mix	0.1%	6	1.4	
Chlorocresol	1% pet.	6	1.4	
Comfeel transparent [®]	as is	6	1.4	
Benzocaine	5% pet.	5	1.2	
Primin	0.01% pet.	5	1.2	
Sorbic acid	2% pet.	5	1.2	
Hexamidine	0.15% water	5	1.2	
Formaldehyde	1% water	4	0.9	
BHA (buylated hydroxyanisole)	2% pet.	4	0.9	
Fusidic acid	2% pet.	4	0.9	
Methylchloroisothiazolinie (and) methylisothiazolinone	0.01% water	3	0.7	
Mercaptobenzothiazole	2% pet.	3	0.7	
Polyethylene glycol 6 and 32	as is	3	0.7	
Imidazolidinyl urea (imidurea)	2% pet.	3	0.7	
EMLA [®] cream	as is	3	Performed on 210 patients	
<i>N</i> -isopropyl- <i>N</i> -phenyl Paraphenylenediamine	0.1% pet.	2	0.5	
Paratertiary butyl phenol formaldehyde resin	1% pet.	2	0.5	
Quaternium-15	1% pet.	2	0.5	
Isopropyl myristate	10% pet.	2	0.5	
Triclocarban	1% pet.	1	0.2	
Disodium EDTA (disodium ethylenediaminetetraacetic acid)	1% pet.	1	0.2	

(Continued)

Table 1. Continued

Test substance	Percentage and vehicle	Number of positive tests	Percentage of sensitized patients (423 patients)	Percentage in a meta-analysis, 1185 patients (1991–2003), Machet et al. (6)
2-bromo-2-nitropropane-1,3-diol (Bronopol)	0.5% pet.	1	0.2	
BHT (butylated hydroxytoluene)	2% pet.	0	0	
Propyl gallate	0.5% pet.	0	0	
Erythromycin	1% pet.	0	0	
Resorcinol	1% pet.	0	0	

Pet., petrolatum.

^aAllergens given in italics are in the European baseline series of contact allergens.

Dijon (74.3 years), but included patients were younger in Strasbourg (67.9 years).

Clinical characteristics of chronic leg ulcers

Their causes were venous insufficiency in 234 cases, arteriovenous in 111 cases, arteritis in 27 cases, necrotizing angiodermatitis in 13 cases, and other causes in 27 cases.

The duration of the ulcers when the patch tests were carried out was <1 year in 240 cases, 1–10 years in 118 cases, and >10 years in 65 cases. According to the causes of the ulcers, there was no difference in the duration of the leg ulcers ($P = 0.166$). With ANOVA table, there was a statistically longer duration declared by patients in Strasbourg (140 months) than in other centres (Nancy: 46.8 months, Dijon: 37.5 months, and Ivry: 30 months). Surrounding eczematous lesions were observed in 315/423 (74%) cases.

Results of patch tests

Centres. Among 423 patients, 73% had at least one positive patch test with no statistically significant difference from one centre to another: 67% in Dijon, 73.5% in Ivry, 73.5% in Strasbourg, and 76% in Nancy. Considering the percentage of sensitized patients, there was no statistically significant difference between the populations included in the four different centres ($\chi^2 = 3.541$, 3df, not significant).

Sensitized patients. The mean number of positive patch tests per person among the 308 sensitized patients was 3.65 tests per patient (1–19 positive patch tests per person). None of these patients had an angry back. The mean number of positive patch tests per patient in the total population (no allergy and at least one allergy detected) was 2.6.

Involved allergens. The most frequently involved allergens (Table 1) were *Myroxylon*

pereirae (41%), fragrance mix I (containing cinnamyl alcohol, cinnamal, amyl cinnamal, hydroxycitronellal, geraniol, eugenol, isoeugenol, and *Evernia prunastri*) (26.5%), lanolin (wool alcohol) and its derivative Amerchol L101[®], respectively, in 17.7% and 19.6%, and colophonium (7.6%). Among antibiotics, patch tests were positive with neomycin (9.2%), gentamycin (2.6%), fusidic acid in four cases (0.95%), and no case with erythromycin. 20.1% of the patients had at least one positive reaction to one or more of the following antiseptics: povidone–iodine, benzalkonium chloride, cetrimide, eosin, chlorhexidine, clioquinol, hexamidine, and triclocarban. With the inclusion of thimerosal, almost 24% of the patients were sensitized to one antiseptic or more. Thirty-four (8%) patients had at least one positive patch test to corticosteroids, mainly with budesonide (7.1%). Positive results were observed with commercial products: Biafine (8.5%), Duoderm E (4%), Comfeel transparent (1.4%), and EMLA cream (1.4% of 210 patients). Among preservatives and antioxidants, the most frequent sensitizations were observed with sodium metabisulfite (3% of the cases), paraben mix (3%), and Euxyl K400[®] (containing methylidibromo glutaronitrile and phenoxyethanol) (2.6%). Excipients led to positive results with cetearyl alcohol (cetostearyl alcohol) (5.7%), sorbitan sesquioleate (4%), propylene glycol (3.5%), triethanolamine (1.7%), polyethylene glycol (0.7%), and isopropyl myristate (0.5%). Rubber accelerators, possibly present in elastic bandages, induced positive reactions with thiuram mix (4.25%), mercapto mix (1.4%), and mercaptobenzothiazole (0.7%). There were no statistically significant differences between the percentage of positivity from one centre to another for all the allergens belonging to the baseline series or to the special series for chronic leg ulcers. Additionally, personal products used by the patients caused positive reactions in patch tests with Algo-plaque HP[®] (URGO, Chenove, France) (three

cases), Askina gel pur[®] (Braun Medical SAS, Boulogne Billancourt, France) (three cases), Ialuset[®] ointment (GENEVRIER SA, Sophia Antipolis, France) (two cases), Allevyn[®] (Smith and Nephew Laboratory, Hull, UK) (two cases), and Dexeryl[®] cream (Laboratoire Pierre Fabre Santé, Boulogne, France) (two cases).

Dependence between allergens. With a chi-squared test with 1df, there was no dependence between the positivity of patch tests between lauryl (dodecyl) gallate and octyl gallate ($\chi^2 = 4.383$), quaternium-15 and benzalkonium chloride ($\chi^2 = 0.233$), tixocortol pivalate and hydrocortisone-17-butyrate ($\chi^2 = 6.978$), and Comfeel transparent and colophonium (rosin). With a chi-squared test with 1df, there was a dependence between the positivity of patch tests with *M. pereirae* and fragrance mix ($\chi^2 = 82.3$), neomycin and gentamycin ($\chi^2 = 39$), colophonium and Duoderm E ($\chi^2 = 66.550$ for <0.0001), lanolin and Amerchol L101 ($\chi^2 = 183.7$), sorbitan sesquioleate and fragrance mix I ($\chi^2 = 17.7$), budesonide and 17-hydrocortisone butyrate ($\chi^2 = 93.2$), and budesonide and tixocortol pivalate ($\chi^2 = 13.817$, $P = 0.0002$).

Frequency of sensitization and duration of the ulcer. According to the duration of the ulcer, the frequency of sensitization was 162/240 (67.5%) in the group <1 year, 93/118 (79%) in the group 1–10 years, and 53/65 (81.5%) in the group >10 years ($\chi^2 = 8$, $P < 0.02$). The mean number of positive tests per patient was statistically significantly different: 2.3 (SD = 2.6) for patients <1 year, 2.9 (SD = 3.1) for 1–10 years, and 3.5 (SD = 3.6) for >10 years ($P = 0.0032$, Fisher's test).

There was an increased number of sensitizations per patient according to the duration of the ulcer with a difference between the group of the <1 year compared with the group >10 years (1.212 positive tests per patient, $P = 0.0032$, Fisher's test), but when concerning the allergens, the order of frequency was almost the same in these two groups, except for corticosteroids (Table 2).

According to the Spearman's rank correlation coefficient, the number of positive tests per patient is correlated with the number of months of the duration of the ulcer. The Spearman's rank correlation test provides a p-value equal to 0.156 ($P < 0.01$), which shows the link between the number of positive tests per patient and the duration of the ulcer.

Sensitization and clinical features. Among patients with a surrounding eczema, 246/315 (78%) patients had at least one sensitization, while 62/108 (57%) patients without surrounding eczema were sensitized; the difference was statistically significant ($\chi^2 = 17.4$, $P < 0.0001$). There was no correlation between the frequency of sen-

sitization and the cause of ulcer as 19/27 (70.4%) of the arterial chronic leg ulcers, 78/110 (71%) of arteriovenous chronic leg ulcers, and 176/233 (75.5%) of venous chronic leg ulcers had at least one positive patch test ($\chi^2 = 6.5$, $P = 0.26$).

Discussion

From this large, prospective, multicentre study, we confirm that contact allergy and polysensitization are very frequent in patients suffering from chronic leg ulcers based on the fact that 73% of our patients had at least one sensitization. This percentage is close to those (72.5%) evaluated by a meta-analysis (6). Contact allergy is more and more frequent, the longer the duration of the ulcer is. From a previous study enrolling 50 patients with chronic leg ulcers (9), in the subgroup with a polyvalent allergy, the mean duration of chronic leg ulcers was significantly longer than in those without polysensitization. There was a link between the number of sensitizations per patient and the duration of the ulcer, suggesting that topical drugs and dressings used for chronic leg ulcers are responsible in inducing the sensitization. We confirm that polysensitization is frequent in patients with chronic leg ulcers as 3.65 tests per patient were positive among the 308 sensitized patients. In most of the previous large studies, the polysensitization was suspected (1–4, 10) but was difficult to demonstrate as some variables could be correlated, especially if the series included commercial dressings containing molecules also belonging to the special series. To reduce that bias, in our series, there were a few commercial ointments or dressings. In spite of that, there is still a bias in the estimation of the percentage of polysensitized patients, which could be enhanced by the dependence found between some molecules or dressings. This was observed not only with colophonium and Duoderm E but also with *M. pereirae* and fragrance mix I, sorbitan sesquioleate and fragrance mix I, neomycin and gentamycin, lanolin and Amerchol L101, and between corticosteroids.

As previously reported (1–4, 6), the most frequent sensitizer was *M. pereirae* even in the group of patients who have had chronic leg ulcers <1 year. This could be because of the persistent practice in France of using tulle with *M. pereirae* to treat wounds (11). In USA, positive patch tests with *M. pereirae*, which have a definite or probable relevance in patients with chronic leg ulcers, are rare (12). *M. pereirae* and fragrance mix I were dependent as previously reported in patients without chronic leg ulcers (13).

Table 2. Percentage of positive reaction for 15 allergens according to the duration of the leg ulcer

	Percentage of positive tests in patients with <1 year duration of the ulcer	Percentage of positive tests in patients with >10 years duration of the ulcer
<i>Myroxylon pereirae</i> (Balsam of Peru)	35.4	52.2
Fragrance mix I	22.9	33.85
Lanolin (wool alcohols)	14.2	23
Benzalkonium chloride	9.2	13.8
Povidone–iodine	9	12.3
Neomycin sulfate	8.8	10.7
Colophonium (colophony)	7.1	7.7
Budesonide	5.4	12.3
Euxyl K400 [®]	3.3	4.6
Propylene glycol	2.5	6.15
Gentamycin	2.1	4.6
Hydrocortisone 17-butyrate	1.25	3.1
Chlorhexidine digluconate	1.25	3.1
Tixocortol pivalate	0.8	4.6
EMLA [®] cream	1 case	0 case

Excipients

Sensitization to sorbitan sesquioleate was observed in 4% of the cases, and there was a correlation between the positivity of sorbitan sesquioleate and fragrance mix I. Wakelin et al. (14) and Pasche-Koo et al. (15) emphasized that sorbitan sesquioleate, that is contained in fragrance mix I, is a frequent sensitizer in patients with chronic leg ulcers. Tavadia et al. (2) reported on the frequency of the sensitization to propylene glycol, with positive patch test in 4% of their patients with chronic leg ulcers. It was observed in 3.5% of our patients, a frequency not so different from those in the general population (16, 17). Sensitization to lanolin is still debated (18), but the high percentage of positive tests does not seem to be accidental because in our patients, there was a statistically significant dependence between patch test positivity to lanolin (17.7%) and Amerchol L101 (19.6%). In a central London teaching hospital patch-tested population, the mean annual rate of sensitivity to lanolin was 1.7% (19).

Antibiotics

Sensitization to aminoglycosides was frequent with dependence between the positivity of patch tests to neomycin and gentamycin, whereas sensitization to fusidic acid was rare. In literature, sensitization to fusidic acid is not very frequent (13, 20), while contact allergy to aminoglycosides is more frequent (13), with cross-sensitizations between aminoglycosides (21) and a possible systemic contact dermatitis if patients are systemically exposed to this antibiotic class later on (22). Therefore, and as aminoglycosides are not necessary to treat chronic leg ulcers, it could be advised to suppress their use.

Antiseptics

This study emphasizes the high percentage of sensitization to antiseptics in patients suffering from chronic leg ulcers. From the German information network of departments of dermatology in non-atopic patients without leg ulcers or stasis dermatitis, contact allergy to chlorhexidine digluconate and benzalkonium chloride were found in, respectively, 0.47% and 0.69% of the tested patients (23), less frequently than observed in our patients tested with the same dilutions. The best concentration to test povidone–iodine has not yet been determined. Patch tests carried out with povidone–iodine diluted at 2% in water would be more specific but less sensitive than those with povidone–iodine at 10% in water (concentration used in this study), which can induce irritation (24–26). In terms of benefit–risk, use of antiseptics in chronic leg ulcers remains highly debatable. In a controlled study (27), with three parallel groups of only 17 patients suffering from at least two similar chronic leg ulcers, povidone–iodine significantly increased the healing rate and reduced the healing time of the chronic leg ulcers. In terms of benefit, only larger double-blind studies with a placebo could demonstrate that antiseptics may have some value in treating chronic leg ulcers.

Corticosteroids

Sensitization to corticosteroids occurred frequently in our study, with positive patch tests in 8% of the patients with chronic leg ulcers. In literature, in the general population of patients having been tested with corticosteroids, only 0.4% to 4% (28–32) had positive patch tests. As class D1 corticosteroids (33) are frequently used in patients with chronic leg ulcers, it could be suggested to add to the series

alclometasone-17,21-dipropionate [1% petrolatum (pet.)] or betamethasone 17-valerate (0.12% pet.), which belong to this chemical class (33). It is not possible to suppress the use of corticosteroids around chronic leg ulcers, but corticosteroid sensitization should be considered when, despite topical steroids, eczema becomes worse or does not improve.

Modern dressings

We observed 17 (4%) cases of sensitization to Duoderm E, with a statistically significant dependence between the positivity of patch tests with colophonium and Duoderm E. Sensitization to colophonium derivatives in hydrocolloid dressings has been reported in eight previous cases (34–36). A contact allergy to Comfeel transparent was found in six cases. Grange-Prunier et al. (37) reported one case of sensitization to Comfeel transparent without any positive reaction in any of the tests of the components given by Coloplast Laboratory. Pasche-Koo et al. (38) reported one case with contact dermatitis to Comfeel hydrocolloid[®] because of a sensitization to carboxymethylcellulose (tested at 10%). From two previously published studies, among 50 patients tested with modern dressings, the sensitization was observed with Intrasisite gel[®] (Smith & Nephew Healthcare Ltd, Hull, UK) (four cases) (4, 39), Varihesive[®] Hydrogel (Convatec, Princeton, NJ, USA) (three cases) (4), Hydrosorb[®] plus (Hatrman International, Heidenheim, Germany) (two cases) (4), Duoderm[®] (Convatec, Princeton, NJ, USA) (two cases) (39), and Iodosorb[®] (Smith & Nephew Healthcare Ltd, Hull, UK) (one case) (39). Intrasisite gel has been reported as inducing positive results in 19/200 patch-tested patients with chronic leg ulcers (2) and in 1 case by Lee and Kim (40). Of our two cases of sensitization to Ialuset ointment, one patient was sensitized to the perfume contained in that topical drug. We also observed sensitization to Algoplaque HP (three cases), Askina gel (three cases), and Allevyn (two cases). Johnsson and Fiskerstrand (41) reported one case of contact urticaria caused by carboxymethylcellulose contained in a hydrocolloid dressing. Manufacturers should be advised to absolutely avoid the use of any colophony derivatives or perfumes in the composition of new dressings. It would also be absolutely necessary to list all the components on their packaging.

It has been recommended to use EMLA cream for the mechanical debridement of leg ulcers. Three of our patients had a positive patch test with it, in addition to one case previously reported by García (42).

Sensitization and clinical characteristics of chronic leg ulcers

There was a statistically significant correlation between the existence of eczematous lesions surrounding the ulcer and the prevalence of contact allergy, even if 57% of the patients without surrounding eczema were sensitized. Contact allergy in leg ulcers is caused by different factors (1): the use of molecules that are strong sensitizers; a repeated and long-lasting contact with molecules under occlusion; and an alteration of the barrier function, which enhances the absorption of sensitizing molecules. Moreover, in venous insufficiency, there is also a local hypervascularization, which favours lymphocyte migration to the skin (43) as well as an increase of the Langerhans' cell number (44). The high risk of sensitization in patients with chronic leg ulcers does not seem to be correlated with the cause of the chronic leg ulcers. According to McFadden and Basketter (45), contact sensitization depends on the presence of irritant signals coming from the allergen itself because of its inherent irritant properties or from the presence of inflammatory chemicals already present on inflamed skin. Both conditions are associated in chronic leg ulcers. The 'danger' signal that may lead to sensitization does not come from the antigen signal alone but also from an associated irritancy (45). Using products with a low irritancy potential could reduce the sensitization potential of dressings in patients with chronic leg ulcers.

In conclusion, patients with chronic leg ulcers have to be tested as they have a very high risk of contact allergy. Their sensitization rate increases with the duration of the chronic leg ulcers. In terms of benefit–risk, it seems advisable to exclude some strong sensitizers from the pharmacopoeia of these patients, for example *M. pereirae*, fragrances, wool alcohol and its derivatives, colophonium and its derivatives, aminoglycosides, and antiseptics. The composition of modern dressings such as hydrocolloids should be given on the packaging. We propose including all the allergens having been found with positive results in more than 1.5% of our cases (Table 3). Considering the recent use of some molecules, we propose suppressing thimerosal, gentamycin, and bufexamac but adding to the series according to the concentrations proposed by De Groot (7): silver sulfadiazine, carboxymethylcellulose, lidocaine hydrochloride, and prilocaine hydrochloride (Table 2). Bacitracin has been reported positive in 30% of 54 patients (13), and it could be added to the series, but it only seems important in USA where this antibiotic is still widely used, in contrast to Europe. A leg ulcer series can be used, but it is crucial to test with the

Table 3. Proposal for an updated special series for investigating patients with chronic leg ulcers, to be added to the European baseline series

Molecule	Percentage and vehicle
Sorbitan sesquioleate	20% pet.
Propylene glycol	10% water
Carboxymethylcellulose	2% pet.
Cetearyl alcohol (cetostearyl alcohol)	20% pet.
Triethanolamine	2.5%
Lauryl gallate (dodecyl gallate)	0.5% pet.
Octyl gallate	0.3% pet.
Euxyl K400® (methyl dibromo glutaronitrile and phenoxyethanol)	0.5% pet.
Sodium metabisulfite	1% pet.
Povidone-iodine	10% water
Benzalkonium chloride	0.1% pet.
Cetrimide	0.1% water
Chlorhexidine digluconate	0.5% water
Silver sulfadiazine	5% pet.
Eosin	50% pet.
Chlorocresol	1% pet.
Amerchol L101®	50% pet.
Bacitracin	5% pet.
Hydrocortisone-17-butyrate	0.1% pet.
Alclometasone-17,21-dipropionate	1% pet.
Lidocaine hydrochloride	5% pet.
Prilocaine hydrochloride	5% pet.

Pet., petrolatum.

products and their ingredients actually used by the patients, including new dressings, corticosteroids, and antiseptics.

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