

The current spectrum of contact sensitization in patients with chronic leg ulcers or stasis dermatitis – new data from the Information Network of Departments of Dermatology (IVDK)

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Summary

Background. Patients with lower leg dermatitis, chronic venous insufficiency or chronic leg ulcers have a high prevalence of contact sensitization.

Objectives. To identify the current spectrum of contact allergens in these patients.

Patients and methods. Data of the Information Network of Departments of Dermatology on 5264 patients with the above diagnoses from the years 2003 to 2014 (study group) were compared with data on 4881 corresponding patients from 1994 to 2003 (historical control group) and with a current control group without these diagnoses (n = 55 510).

Results. Allergic contact dermatitis was diagnosed less frequently in the study group than in the historical control group (25.9% versus 16.9%; $p < 0.001$), and contact sensitization to most allergens had declined. The allergen spectrum, however, was largely unchanged. Important allergens are *Myroxylon pereirae* (balsam of Peru) (14.8% positive reactions), fragrance mix I (11.4%), lanolin alcohol (7.8%), colophonium (6.6%), neomycin sulfate (5.0%), cetearyl alcohol (4.4%), oil of turpentine (3.1%), and paraben mix (2.6%). Patch testing with additional series showed sensitization to Amerchol L-101 (9.7%), *tert*-butyl hydroquinone (8.7%), framycetin sulfate (5.0%), and gentamicin sulfate (3.1%).

Conclusions. Topical preparations for treating the above-mentioned conditions should not contain fragrances, *Myroxylon pereirae*, and colophonium. The special allergen spectrum has to be considered in patch testing.

Key words: chronic leg ulcer; chronic venous insufficiency; contact sensitization; patch testing.

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Introduction

Assessment of the wound surroundings represents an essential part of the evaluation of chronic wounds on the lower leg. When eczematous skin lesions occur, both irritant and allergic contact dermatitis have to be considered, and patch testing should be performed for confirmation or exclusion of contact allergy. Irritant contact dermatitis surrounding the wound, owing to exudate, is frequent. It has to be distinguished from allergic contact dermatitis caused by a specific contact allergen in wound dressings, ointments, or other topical treatment agents. Contact

allergy should be considered when dermatitis is recalcitrant even though exudate management is optimized.

In the predominantly elderly patients, peculiar sensitization profiles have to be taken into consideration (1). A comparison of sensitization prevalences in patients with leg ulcers from 25 selected studies between 1975 and 2003 showed a significant increase in sensitization, especially to topical treatments, between two different time periods (2). In contrast, other studies have described a decrease in contact sensitization frequency (3). The occurrence of allergic contact dermatitis in patients with chronic leg ulcers is associated with a prolonged course of healing and increased treatment costs (4). The spectrum of contact sensitization in chronic leg ulcer patients has been described in several studies in the past (2–14). Worldwide, the most frequent contact allergens in this group of patients during the last 20–40 years were *Myroxylon pereirae* (balsam of Peru), fragrances, colophonium, neomycin (and framycetin) salts, lanolin alcohol, Amerchol L 101, benzocaine, and parabens, with varying clinical relevance. We intended to identify the current spectrum of contact sensitization in chronic leg ulcer patients based on data of the Information Network of Departments of Dermatology (IVDK), 2004–2013, and to compare these data with corresponding data of the preceding 10-year period, to evaluate possible changes.

Patients and Methods

The IVDK addresses the epidemiology of contact allergy. Currently, 56 departments of dermatology in Germany, Switzerland and Austria are included in the network. Its structure and routine operating procedures have been described in detail elsewhere (15). Briefly, patients' histories, including clinical data such as diagnoses and localizations, and patch test results of all patients in the participating centres, are documented in a standardized way, recorded in local databases, and, after anonymization, transmitted to the IVDK central office at the University Medical Centre Göttingen twice yearly. After passing a quality control check, data are added to the central IVDK database and analysed according to published guidelines (16, 17). During the years 2004–2013, 114 442 patients were patch tested in the IVDK. From these, a case group was selected with 'stasis dermatitis/chronic leg ulcer' as the main diagnosis and/or the leg/lower leg as the main localization, with chronic venous insufficiency as a comorbidity. These 5264 patients (4.6%) are referred to as the CLU group. Furthermore, we defined a historical control group, using the same criteria as above, including the years 1994–2003 (chronic leg

ulcer patients 1994–2003), which yielded 4881 patients (5.6% of the total of 87 896 patients tested). To analyse which of the ubiquitous contact allergens present in the baseline series are currently specifically associated with stasis dermatitis/chronic leg ulcer, we defined a current control group (2004–2013). This group comprised patients without stasis dermatitis/chronic leg ulcer, without leg/lower leg localization, and without chronic venous insufficiency. As the CLU group has a special age spectrum, with 90% of the patients being aged 48–88 years, the current control group was restricted to this age range, because age is strongly associated with sensitization (1). The current control group consisted of 55 510 patients.

All members of the IVDK are also members of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe; DKG). Patch tests are performed and read according to DKG guidelines (18). For this data analysis, patch test reactions on day (D) 3 were selected. D4 readings were chosen only in exceptional cases, when a reading was performed on D4 instead of D3. Readings coded as +, ++ or +++, that is, positive reactions with erythema, infiltration, papules, and/or (coalescing) vesicles, according to the ICDRG scoring (19), were rated as positive in dichotomized analyses. Patch test preparations were purchased from Almirall Hermal, Reinbek, Germany. The patch test exposure time was 48 h in 83% of patients, and 24 h in 17% of patients. With a few (temporary) exceptions, Finn Chambers® (inner diameter of 8 mm) on Scanpor® tape were used as test chambers.

The statistical significance ($p < 0.05$) of differences in sensitization frequencies between the CLU group and the control groups was determined by the use of non-overlapping 95% confidence intervals of the relative reaction frequencies. Differences in proportions of special characteristics among different subgroups of patients were statistically tested with the χ^2 -test. A p -value of < 0.05 was regarded as significant. Data were managed and analysed with the statistical software SAS®, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Table 1 shows a comparative description of the three subgroups of patients, addressing population characteristics that may influence patch test outcomes. The sex distribution was similar in all patient groups, within a narrow range of variation. The age distributions of the two CLU groups were also very similar. The current control group, however, had a different distribution, with a peak in younger years, even though the total age

Table 1. Description of the study group [chronic leg ulcer (CLU) group], the historical control group (CLU patients from 1994 to 2003), and the current control group

	CLU group (n = 5264)	CLU patients 1994–2003 (n = 4881)	Current control group (n = 55 510)
Male patients (%)	40.0	33.5	35.0
Age distribution (years): Q25–median–Q75*	65–73–80	62–72–79	54–60–69
Atopic dermatitis (past or present) (%)	3.3	1.5	14.0
Reason for patch test: contact sensitization to be excluded (%)	54.8	54.9	36.3
Suspected allergen sources†: cosmetics, body care products, topical drug preparations, rubber items (%)	53.5	33.4	35.7
	70.6	81.5	19.0
	12.9	10.7	5.1
Final diagnosis: stasis dermatitis/CLU, allergic contact dermatitis (%)	71.4	63.3	0‡
	16.9	25.9	23.4

For details, see text.

*Q25 = 25% quantile; Q75 = 75% quantile.

†Multiple answers possible.

‡Owing to group definition.

range was restricted according to the CLU group. Past or present atopic dermatitis was strikingly more prevalent in the current control group (14.0%) than in the CLU groups (3.3% and 1.5%, respectively). What seems most important - concerning the frequency of positive patch test reactions - are the differences in indication for patch testing, suspected allergen sources, and final diagnoses. While more than half of the patients of the CLU groups were tested in order to rule out contact sensitization, this was the case in only about one third of the patients of the current control group (significant difference; $p < 0.0001$). Although the proportions of patients tested on these premises were almost identical in the two CLU groups (54.8% and 54.9%, respectively), allergic contact dermatitis was diagnosed significantly more frequently in the historical CLU control group than in the study group (25.9% versus 16.9%; $p < 0.001$). Cosmetics and body care products were significantly more often suspected as allergen sources among the patients in the study group than in the historical CLU control group (53.5% versus 33.4%; $p < 0.001$). The opposite was true for topical drugs (70.6% versus 81.5%; $p < 0.001$).

The DKG baseline series was patch tested in 99% of the chronic leg ulcer patients (both groups), and in 90% of the control group, allowing an unbiased comparison of reaction frequencies between the three subgroups of patients (Table 2). In contrast, the proportions of patients tested with all other, special, test series, were so divergent that reaction frequencies are probably biased by the individual indications for patch testing with these series. (For instance, 9.8% of patients in the control group but 22% of

those in the CLU group were tested with the corticosteroid series.) Therefore, we only present reaction frequencies with these series in the CLU group (Table 3), without comparison with the control groups.

In total, 2333 patients (44.8% of 5202) in the CLU group had at least one positive reaction to an allergen of the DKG baseline series, as compared with 2824 of 4816 (58.6%) chronic leg ulcer patients from 1994 to 2003, and 21 496 of 49 871 (43.1%) in the current control group. Thus, this proportion was significantly lower in the CLU group than in chronic leg ulcer patients from 1994 to 2013 ($p < 0.001$).

A comparison of the frequency of positive reactions to allergens of the baseline series is shown in Table 2. In the CLU group, significantly more positive reactions were seen to *M. pereirae* (balsam of Peru), fragrance mix I, lanolin alcohol, fragrance mix II, colophonium, neomycin sulfate, cetearyl alcohol, jasmine absolute, ammoniated mercury, oil of turpentine, *Santalum album* (sandalwood) oil, benzocaine, paraben mix, bronopol, and zinc diethyldithiocarbamate than in the current control group. With two exceptions, namely ammoniated mercury and bronopol, positive reactions to these allergens were observed significantly less frequently in the current CLU group than in the chronic leg ulcer patients from 1994 to 2003. In addition, significant decreases in sensitization to propolis, bufexamac and formaldehyde were noted in current chronic leg ulcer patients, as compared with such patients from 1994 to 2003.

Table 2. Reaction frequencies (percentage of positive reactions) for allergens of the baseline series, supplemented with 95% confidence intervals (CIs). Significant differences in terms of more positive reactions in the CLU group, as compared with one of the control groups, are in bold type. The vehicle was pet. unless otherwise indicated

Substance	Test concentration	CLU group (n = 5202 tested with the DKG baseline series)	CLU patients 1994–2003 (n = 4816 tested with the DKG baseline series)	Current control group (n = 49 871 tested with the DKG baseline series)
<i>Myroxylon pereirae</i> (balsam of Peru)	25%	14.8 (13.8–15.8)	23.9 (22.7–25.2)	9.8 (9.6–10.1)
Fragrance mix I	8%	11.4 (10.5–12.3)	19.5 (18.4–20.7)	10.0 (9.7–10.3)
Lanolin alcohol	30%	7.8 (7.0–8.5)	19.2 (18.1–20.4)	2.0 (1.8–2.1)
Fragrance mix II	14%	6.8 (6.1–7.6)*	NT	5.7 (5.5–6.0)*
Colophonium	20%	6.6 (5.9–7.3)	8.1 (7.3–8.9)	4.0 (3.8–4.2)
Methyldibromo glutaronitrile	0.3%	6.1 (5.1–7.3)*	7.5 (6.3–8.8)*	5.3 (5.0–5.7)*
Methyldibromo glutaronitrile	0.2%	3.8 (3.2–4.6)*	NT	3.2 (3.0–3.4)*
Nickel sulfate	5%	5.2 (4.6–5.9)	5.5 (4.9–6.2)	11.6 (11.3–11.9)
Neomycin sulfate	20%	5.0 (4.3–5.9)*	9.2 (8.4–10.1)	2.4 (2.2–2.7)*
Cetearyl alcohol	20%	4.4 (3.9–5.0)	7.5 (6.8–8.3)	0.7 (0.6–0.8)
Propolis	10%	3.8 (3.3–4.4)	5.6 (5.0–6.4)	3.3 (3.1–3.4)
<i>Cananga odorata</i> [Ylang-ylang (I + II)] oil	10%	3.8 (3.0–4.8)*	NT	2.8 (2.6–3.1)*
<i>Jasminum</i> spp. extract (jasmine absolute)	5%	3.6 (2.8–4.5)*	NT	1.6 (1.5–1.8)*
Ammoniated mercury chloride	1%	3.6 (2.7–4.9)*	3.1 (2.6–3.6)	2.1 (1.9–2.3)*
Potassium dichromate	0.5%	3.5 (3.0–4.0)	3.1 (2.6–3.7)	4.6 (4.4–4.7)
Oil of turpentine	10%	3.1 (2.6–3.6)	4.3 (3.7–4.9)	2.0 (1.8–2.1)
<i>Santalum album</i> (sandalwood) oil	10%	3.1 (2.4–3.9)*	NT	1.4 (1.3–1.6)*
Benzocaine	5%	3.0 (2.3–3.9)*	5.1 (4.5–5.8)	1.4 (1.2–1.6)
Thiuram mix	1%	2.8 (2.3–3.3)	3.7 (3.2–4.3)	2.1 (2.0–2.3)
Paraben mix	16%	2.6 (2.2–3.1)	5.6 (5.0–6.3)	0.8 (0.8–0.9)
Bronopol	0.5%	2.4 (2.0–2.8)	2.1 (1.6–2.5)	1.1 (1.1–1.2)
Cobalt chloride	1%	2.4 (2.0–2.8)	2.8 (2.3–3.3)	4.5 (4.3–4.7)
Methylchloroisothiazolinone/methylisothiazolinone	0.01% aq.	2.2 (1.8–2.7)	2.3 (1.9–2.8)	3.4 (3.2–3.6)
Compositae mix	5%	1.9 (1.4–2.5)*	NT	1.7 (1.6–1.9)*
Zinc diethyldithiocarbamate	1%	1.4 (1.1–1.8)	1.1 (0.8–1.4)	0.5 (0.5–0.6)
Bufexamac	5%	1.4 (1.1–1.7)	3.7 (3.1–4.3)*	1.0 (0.9–1.1)
Compositae mix II	5%	1.3 (0.6–2.4)*	NT	2.0 (1.7–2.3)*
Iodopropynyl butylcarbamate	0.2%	1.1 (0.8–1.5)*	0.6 (0.1–2.1)*	1.4 (1.3–1.5)*
Formaldehyde	1% aq.	1.0 (0.8–1.4)	1.8 (1.5–2.2)	1.2 (1.1–1.3)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5%	0.9 (0.7–1.2)	NT	2.7 (2.6–2.9)
Epoxy resin	1%	0.8 (0.6–1.1)	0.5 (0.3–0.8)	1.6 (1.5–1.8)
<i>p</i> -tert-Butylphenol formaldehyde resin	1%	0.7 (0.5–1.0)	1.3 (1.0–1.6)	0.7 (0.6–0.7)
<i>N</i> -isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylenediamine	0.1%	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.7 (0.7–0.8)
Mercapto mix (without mercaptobenzothiazole)	1%	0.5 (0.4–0.8)	0.7 (0.5–1.0)	0.6 (0.5–0.7)
Mercaptobenzothiazole	2%	0.4 (0.3–0.7)	0.5 (0.3–0.9)	0.6 (0.5–0.7)

CLU, chronic leg ulcer; DKG, German Contact Dermatitis Research Group; NT, not tested as part of the baseline series during the respective time period.

*A reduced number of tested patients because an allergen preparation was not part of the baseline series throughout the whole study period; the percentage shown is related to the number of subjects tested with that particular allergen.

Additional DKG test series were patch tested in the CLU group, with varying frequencies. The results are summarized in Table 3, in which only those allergens are mentioned that elicited positive reactions in at least 1% of the patients tested. The DKG series 'antimycotic drugs' was patch tested in 1319 (current) chronic leg ulcer patients. Of these, 0.5% reacted to nystatin 2% pet., and 0.4% to clotrimazole 5% pet.

An analysis of concomitant reactions gave the following results. Lanolin alcohol 30% pet. and Amerchol L-101 50% pet. were patch tested in parallel in 4580 patients. Of these, 440 (9.6%) reacted to Amerchol L-101, and 357 (7.8%) to lanolin alcohol. Two hundred and thirty-eight patients reacted to both allergen preparations, representing 54% of those reacting to Amerchol L-101, and 67% of those reacting to lanolin

Table 3. Reaction frequencies (percentage of positive reactions) for allergens of additional German Contact Dermatitis Research Group (DKG) test series in the current chronic leg ulcer (CLU) group

Patch test series (number of patients tested) and allergen preparations	Test concentration	Percentage of patients with positive reactions
DKG ointment base series (n = 4756)		
Amerchol L-101	50%	9.7
<i>tert</i> -Butyl hydroquinone	1%	8.7
Propylene glycol	20% aq.	3.9
Cocamidopropyl betaine	1% aq.	2.6
Octyl gallate	0.3%	2.3
HA (butylated hydroxyanisole)	2%	1.4
DKG preservative series (n = 4216)		
Methylisothiazolinone*	0.05% aq.	1.7
Chloroacetamide	0.2%	1.4
DKG topical antibiotics (n = 2029)		
Framycetin sulfate	10%	5.0
Gentamicin sulfate	20%	3.1
Fusidic acid, sodium salt	2%	2.3
Bacitracin	20%	1.3
DKG disinfectant series (n = 1944)		
Povidone iodine	10% aq.	10.3
Benzalkonium chloride	0.1%	1.7
DKG additional topical drugs (n = 1782)		
<i>Arnica</i> blossom extract*	0.5%	5.1
Clioquinol	5%	1.0
DKG rubber series (n = 1229)		
<i>p-tert</i> -Butylcatechol	0.25%	4.2
Tetraethylthiuram disulfide	0.25%	3.6
1,3-Diphenylguanidine	1%	3.4
Dipentamethylenethiuram disulfide	0.25%	2.7
Tetramethylthiuram disulfide	0.25%	2.3
Zinc diethyldithiocarbamate	1%	2.0
Tetramethylthiuram monosulfide	0.25%	1.3
DKG corticosteroids (n = 1133)		
Budesonide	0.10%	3.4
Tixocorol-pivalate*	1.0%	1.9
Amcinonide	0.10%	1.3
Hydrocortisone-17-butyrate	0.10%	1.2

Note that the number of individuals tested with the different specific patch test series varied, which may have affected reaction prevalence rates. Only allergens eliciting positive reactions in at least 1% of the patients are listed. The vehicle was pet., unless otherwise indicated.

*A reduced number of tested patients because an allergen preparation was not part of the respective test series throughout the whole study period.

alcohol. Lanolin alcohol 30% pet. and cetearyl alcohol 20% pet. were patch tested in 5062 patients, of whom 393 (7.8%) reacted to lanolin alcohol, and 220 (4.3%) to cetearyl alcohol. Those 76 patients reacting to both represent 19% of those reacting to lanolin alcohols, and 35% of those reacting to cetearyl alcohol. Neomycin sulfate 20% pet. and framycetin sulfate 10% pet. were patch tested in 1985 patients, of whom 99 (5.0%) reacted to framycetin, and 98 (4.9%) to neomycin. Seventy-nine patients were sensitized to both antibiotics, representing 80% of those sensitized to either of them. Neomycin sulfate 20% pet. and gentamicin sulfate 20% pet. were tested in 2345 patients. Of these, 117 (5.0%) reacted

to neomycin, and 71 (3.0) to gentamicin. Thirty-four patients reacted to both allergens, representing 48% of those sensitized to gentamicin, and 29% of those sensitized to neomycin.

Discussion

Comparison with chronic leg ulcer patients from 1994 to 2003

Although the indication for patch testing did not change between the two periods (1994–2003 versus 2004–2013: 55% 'contact sensitization to be excluded'),

the frequency of allergic contact dermatitis as a final diagnosis significantly declined from 25.9% to 16.9%. A limiting factor is the absence of routine D7 readings, which may have led to a slight underestimation of the true frequency of sensitization. However, as these late responses would have been missed in both groups, this does not bias the comparison.

The additional finding that the proportion of patients with at least one positive reaction to an allergen of the DKG baseline series significantly declined (from 58.6% to 44.8%) points towards a decrease in the frequency of contact allergies in this vulnerable group of patients. It seems as though the treatment of chronic leg ulcer/stasis dermatitis could have improved from the allergological point of view: fewer patients are sensitized by topical preparations, and/or they are patch tested earlier. This may be interpreted as a sign of increasing awareness of this issue among healthcare professionals and patients with chronic wounds, and is in concordance with trends in other countries (3). However, patch testing of routine substances included in established test series will not identify new allergens (e.g. in novel wound-dressing materials). Therefore, additional testing of patients' own products as the only way of finding new allergens is recommended (19). As patch test results with patients' own materials (e.g. topical drugs and wound dressings) are stored as plain text in the IVDK database, which makes data analysis very difficult in thousands of patients, we abstained from analysing these data for the time being. As another limiting factor of our study, no data on the pathogenesis of the leg ulcers and their duration are routinely documented in the IVDK dataset.

Current allergen spectrum

The comparison of data on chronic leg ulcer patients with the current control group allows the evaluation of the specific contact allergen spectrum in chronic leg ulcer patients. This includes fragrances, *M. pereirae* (balsam of Peru), lanolin alcohol, colophonium, oil of turpentine, neomycin (with cross-reaction to framycetin) sulfate, parabens, some other preservatives, and zinc diethyldithiocarbamate, in part confirming the results from other studies (5, 7, 8, 10, 12, 20). However, our data and those from the literature concerning the allergen spectrum of chronic leg ulcer patients are not always directly comparable, owing to different study designs in terms of different inclusion/selection criteria for patients, regional differences in patch test series, regional and temporal differences, and preferences in therapy. Therefore, varying selection processes need to be taken into account in the interpretation of sensitization prevalence rates published in different studies (5, 7, 8, 10, 12, 20).

Possible allergen sources for the above-mentioned contact allergens are body and wound care products, topical treatments, or elastic stockings (rubber), to which the skin of chronic leg ulcer patients can be exposed in many ways: Whereas adhesive parts of wound dressings may contain colophonium, topical preparations containing oil of turpentine were formerly used in traditional antiseptic and antiinflammatory medicines for wound care, and are still being used in some commercially available products for similar purposes (e.g. in Germany: Ilon® Salbe Classic, Ilon® Protect Salbe, and Ilon® Abszess Salbe). Furthermore, as a source of sensitization, an alcoholic liniment (Spiritus vini gallici), which had frequently been used in elderly care in Germany, may be considered: it contains juniper oil, pine needle oil and similar extracts containing the same sensitizing terpenes as oil of turpentine (21). *tert*-Butyl hydroquinone and BHA (butylated hydroxyanisole) are being used as antioxidants in medical ointments, cosmetics, and foods, and *p*-*tert*-butylcatechol is being used as an antioxidant in rubber production. A recent review on the product composition of 3280 topical pharmaceutical products marketed in Belgium showed that 10% contained at least one of 66 fragrances (22). Fragrances and plant extracts (including Compositae, e.g. *Arnica*), the presence of which is, in most cases, unnecessary, contribute to iatrogenic allergic contact dermatitis in patients with chronic wounds (22). Consequently, care products and medical ointments used in chronic leg ulcer patients should be free of fragrances and Compositae extracts. Against this background, it is difficult to understand why a product such as Peru Lenicet Salbe®, containing lanolin, *M. pereirae* (balsam of Peru), and colophonium, is still on the German market.

Special remarks on the allergen spectrum

In the presented data, the high frequency of positive reactions to so-called 'problematic allergens' (23), such as lanolin alcohol 30% pet., Amerchol L-101 50% pet., propylene glycol 20% aq., cocamidopropyl betaine 1% aq., octyl gallate 0.3% pet., povidone iodine 10% aq., benzalkonium chloride 0.1% pet., and 1,3-diphenylguanidine 1% pet., is remarkable. Although sensitization to these contact allergens seems plausible, in view of the special exposure in chronic leg ulcer patients, the possibility of false-positive reactions has to be considered, and clinical relevance should be thoroughly checked in every single individual case (23).

A positive reaction to paraben mix does not necessarily indicate contact sensitization to parabens: investigations with breakdown tests showed that only half of the

patients reacting to the mix also reacted to single parabens (24). In addition, the well-known 'paraben paradox' has to be considered: patients may react to parabens applied to lower leg skin surrounding a chronic leg ulcer, but tolerate them on healthy skin (25). A similar phenomenon has been described as the 'lanolin paradox', meaning that some sensitized patients do not tolerate lanolin alcohol on inflamed skin, particularly on areas of lower leg (stasis) dermatitis, but tolerate lanolin alcohol in body care products used on healthy skin in other locations (26). This discrepancy may also be explained by different grades of purity used by the cosmetic and pharmaceutical industry. Lanolin alcohol is a natural mixture of emulsifying alcohols of various chain lengths and structures, and they are weak haptens contained in wool fat or wool wax (lanolin) produced from sheep wool (27). Efforts have been made to reduce allergenicity, for example by limiting the concentration of alcohols in lanolin or generally improving purification (27, 28). Testing of a series of anhydrous and hydrogenated lanolin preparations did indeed show that the frequency of sensitivity decreased with every stage of purification (28). In contrast, modification in terms of hydrogenation historically increased the allergenic potential (27, 28).

Conclusion

Allergic contact dermatitis of the skin surrounding the wound delays the healing of ulcers (29) and may also negatively affect the quality of life and the cost of ulcer treatment. Therefore, topical medical treatments and care products should be free of substances identified as frequent contact allergens, such as fragrances, *M. pereirae* (balsam of Peru), or colophonium. Early patch testing for identification of contact allergies is necessary for early avoidance of these. Test series tailored for patients with chronic wounds should take into account the peculiar sensitization profiles of this group of patients as outlined by our data, including modern wound dressings, which may contain contact allergens despite claims of their

'hypoallergenicity'. Additional testing of patients' own products is recommended.

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References

- Mahler V. Contact allergies in the elderly. *Hautarzt* 2015; **73**: 665–673.
- Machet L, Couhe C, Perrinaud A et al. A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. *Br J Dermatol* 2004; **150**: 929–935.
- Katsarou-Katsari A, Armenaka M, Katsenis K et al. Contact allergens in patients with leg ulcers. *J Eur Acad Dermatol Venereol* 1998; **11**: 9–12.
- Lehnen M, Kohaus S, Korber A et al. Contact allergies in patients with chronic wounds: results of a study from 1999 to 2004. *Hautarzt* 2006; **57**: 303–306, 308.
- Barbaud A, Collet E, Le Coz C J et al. 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. *Contact Dermatitis* 2009; **60**: 279–287.
- Beliauskienė A, Valiukeviciene S, Sitkauskienė B et al. Contact sensitization to the allergens of European baseline series in patients with chronic leg ulcers. *Medicina (Kaunas)* 2011; **47**: 480–485.
- Lange-Ionescu S, Pilz B, Geier J, Frosch P J. Kontaktallergien bei Patienten mit Stauungsdermatitis oder Ekzem der

- Beine. *Derm Beruf Umwelt* 1996; **44**: 14–22.
- 8 Reich-Schupke S, Kurscheidt J, Appelhans C et al. Patch testing in patients with leg ulcers with special regard to modern wound products. *Hautarzt* 2010; **61**: 593–597.
 - 9 Reichert-Penetrat S, Barbaud A, Weber M, Schmutz J L. Leg ulcers. Allergologic studies of 359 cases. *Ann Dermatol Venereol* 1999; **126**: 131–135.
 - 10 Renner R, Wollina U. Contact sensitization in patients with leg ulcers and/or leg eczema: comparison between centers. *Int J Low Extrem Wounds* 2002; **1**: 251–255.
 - 11 Smart V, Alavi A, Coutts P et al. Contact allergens in persons with leg ulcers: a Canadian study in contact sensitization. *Int J Low Extrem Wounds* 2008; **7**: 120–125.
 - 12 Tavadia S, Bianchi J, Dawe R S et al. Allergic contact dermatitis in venous leg ulcer patients. *Contact Dermatitis* 2003; **48**: 261–265.
 - 13 Valois A, Waton J, Avenel-Audran M et al. Contact sensitization to modern dressings: a multicentre study on 354 patients with chronic leg ulcers. *Contact Dermatitis* 2015; **72**: 90–96.
 - 14 Zmudzinska M, Czarnecka-Operacz M, Silny W. Contact allergy to glucocorticosteroids in patients with chronic venous leg ulcers, atopic dermatitis and contact allergy. *Acta Dermatovenereol Croat* 2008; **16**: 72–78.
 - 15 Schnuch A, Geier J, Lessmann H et al. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy* 2012; **67**: 847–857.
 - 16 Uter W, Schnuch A, Gefeller O. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**: 47–56.
 - 17 Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes 'Informationsverbund Dermatologischer Kliniken' (IVDK). *Derm Beruf Umwelt* 2005; **53**: 107–114.
 - 18 Schnuch A, Aberer W, Agathos M et al. Performing patch testing with contact allergens. *J Dtsch Dermatol Ges* 2008; **6**: 770–775.
 - 19 Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015; **73**: 195–221.
 - 20 Zmudzinska M, Czarnecka-Operacz M, Silny W, Kramer L. Contact allergy in patients with chronic venous leg ulcers – possible role of chronic venous insufficiency. *Contact Dermatitis* 2006; **54**: 100–105.
 - 21 Schubert S, Bauer A, Molin S et al. Occupational contact sensitization in female geriatric nurses. Data of the Information Network of Departments of Dermatology (IVDK). *J Eur Acad Dermatol Venereol* 2016 (in print).
 - 22 Nardelli A, D'Hooghe E, Drieghe J et al. Allergic contact dermatitis from fragrance components in specific topical pharmaceutical products in Belgium. *Contact Dermatitis* 2009; **60**: 303–313.
 - 23 Geier J, Weisshaar E, Lessmann H et al. Bewertung von Epikutantestreaktionen auf 'Problemallergene' mit vermehrt fraglichen oder schwach positiven Reaktionen. *Derm Beruf Umwelt* 2010; **58**: 34–38.
 - 24 Uter W, Schnuch A, Geier J, Agathos M. Epikutantest-Reaktionen auf Paraben-Mixe und ihre Aufschlüsselungen. Studien der DKG und des IVDK, 1990–2000. *Allergologie* 2002; **25**: 194–202.
 - 25 Fisher A A. The parabens: paradoxical preservatives. *Cutis* 1993; **51**: 405–406.
 - 26 Wolf R. The lanolin paradox. *Dermatology* 1996; **192**: 198–202.
 - 27 Uter W, Spiewak R, Cooper S M et al. Contact allergy to ingredients of topical medications: results of the European Surveillance System on Contact Allergies (ESSCA), 2009–2012. *Pharmacoepidemiol Drug Saf* 2016; **25**: 1305–1312.
 - 28 Sugai T, Higashi J. Hypersensitivity to hydrogenated lanolin. *Contact Dermatitis* 1975; **1**: 146–157.
 - 29 Wilson C L, Cameron J, Powell S M et al. High incidence of contact dermatitis in leg-ulcer patients – implications for management. *Clin Exp Dermatol* 1991; **16**: 250–253.