Review

Contact dermatitis: An important consideration in leg ulcers

Afsaneh Alavi, MD, MSc a, Alina Goldenberg, MD, MSc b, Sharon Jacob, MD c, Amanda Shelley, MD a,⇑, Robert S Kirsner, MD, PhD d

a Division of Dermatology, University of Toronto, Toronto, Ontario, Canada
b Medical Group of North County, Scripps Affiliated Medical Group, Oceanside, CA, United States
c Department of Medicine and Pediatrics (Dermatology), University of California, Riverside, CA, United States
d Department of Dermatology, University of Miami, Miami, FL, United States

Article info

Article history:
Received 24 August 2020
Received in revised form 6 December 2020
Accepted 17 December 2020

Keywords:
Contact dermatitis
Leg ulcers
Chronic wounds
Patch test
Allergic
Irritant

Abstract

The prevalence of chronic wounds is increasing with the aging population, with 1% to 2% of the world-wide population experiencing leg ulcers and positive patch tests reported in up to 75% of this population. With the introduction of modern dressings and compression therapies, clinicians should be cognizant of the potential risk of contact dermatitis in patients with leg ulcers. Contact dermatitis (both allergic and irritant) to wound products may present as maceration, pain, and overall impaired wound healing. Herein, we review the literature on contact dermatitis to wound-care products.

© 2020 Published by Elsevier Inc. on behalf of Women’s Dermatologic Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

Introduction ................................................................. 299
Differentiation of allergic from irritant contact dermatitis ................................................................. 299
Critical utilization of patch testing for allergic contact dermatitis ......................................................... 300
Identification of specific allergen in wound-care dressings and cross reactions ......................................................... 300
Hydrogels .................................................................. 300
Hydrocolloids .......................................................... 300
Calcium alginites and hydrofiber dressings ......................................................................................... 301
Foams ........................................................................ 301
Antiseptics and antibiotics ........................................ 301
Natural and alternative treatments ........................................ 302
Treatment of inflammation and dermatitis .................................................................................. 302
Conclusions .............................................................. 302
Conflicts of interest ................................................ 302
Funding ................................................................. 302
Study approval ......................................................... 302
References ................................................................. 302

⇑ Corresponding author.
E-mail address: ashel050@uottawa.ca (A. Shelley).

https://doi.org/10.1016/j.jiwd.2020.12.010
2152-6475/© 2020 Published by Elsevier Inc. on behalf of Women’s Dermatologic Society.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Introduction

The impact of both allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD) on wound care is not often acknowledged. Concurrent or secondary contact dermatitis (CD) within a nonhealing wound can be a diagnostic and treatment challenge, as well as a major impediment to healing. Wound-care providers must be cognizant of how to recognize and treat CD within nonhealing leg ulcers and other wounds.

CD is an umbrella term for a group of conditions that develop as a result of primary exposure of the skin to substances in the individual’s environment. ACD is a delayed immunologic response to a hapten that requires prior sensitization and elicitation on subsequent exposure to the same hapten. ICD is a direct cutaneous response to injury from friction, chemicals (acids, alkalis, detergents, or solvents), or environmental factors (e.g., prolonged water contact). Many substances can become sensitizing haptens and ultimately allergens, including personal care and medical care products found at work or home, in addition to a wide range of physical items, such as jewellery, watches, shoes, masks, dyes, and gloves (Mowad et al., 2016). Wound-care products are composed of several potentially sensitizing allergens and present a significant risk of causing CD. Over recent years, the number of available wound dressings and antiseptics has increased. Notably, there are currently >5000 wound-care products on the U.S. market (Shah, 2011).

Clinicians should consider CD in cases of dermatitis in the periwound area, or the area under compression. In eczematous skin, both ACD and ICD can present as inflammation, but CD in the indurated periwound area may present with maceration, pain, burning sensation, and impaired healing (Freise et al., 2008; Machet et al., 2004).

Patients with chronic nonhealing wounds are at a higher risk of developing CD because they have lost the protective skin barrier that blocks the absorption of haptens (Freise et al., 2008; Machet et al., 2004). Patients with leg ulcers have been reported to have a positive patch test reaction of 2.21 per patient with a leg ulcer (Marasovic and Vuksic, 1999; Renner and Wollina, 2002). The percentage of sensitization in patients with leg ulcers varies from 46% to as high as 82.5%, with a 33% to 64% increased rate of contact sensitization in the elderly (Balato et al., 2011; Smart et al., 2008; Valois et al., 2015). Patients with chronic leg ulcers often acquire sensitization to what are considered relatively weak allergens owing to frequent use on an impaired barrier. For example, parabens have low sensitization potential on normal skin, but the risk of sensitization in patients with leg ulcer was reported as 11 times greater than in individuals without an ulcer. The major sources of parabens in this population are ointments and gauze dressings (Renner and Wollina, 2002). Likewise, neomycin is a common contact allergen with increased risk of sensitization in the elderly population (9.9-fold). In patients age > 65 years with a chronic leg ulcer, the risk of sensitization to neomycin is 19-fold higher compared with those who are younger (Katsarou-Katsari et al., 1998; Renner and Wollina, 2002).

The aim of this paper is to provide a review of CD to common wound-care products, how to differentiate ACD from ICD, and how to identify specific allergens through patch testing.

Differentiation of allergic from irritant contact dermatitis

Classically, CD is divided into two major categories of ICD and ACD, with the majority (>80%) of reactions being irritant in nature (Bologna et al., 2014). Evidence garnered regarding the pathophysiologic development of both processes has shed light onto why ICD often predates ACD (Imbesi et al., 2011). ICD is a prototype of innate immunity due to direct contact of the skin with a toxic chemical (Imbesi et al., 2011). Any chemical could be considered a potential irritant if it is in direct and prolonged contact with the skin, and the strength of the irritant depends on the chemical nature and concentration of the compound, the vehicle, whether there is occlusion, temperature, and the inherent barrier function of the skin (Fig. 1; Imbesi et al., 2011).

Of note, acute ICD classically occurs acutely within minutes to hours after exposure. In delayed irritant reactions, the reactions can present as late as 8 to 48 hours. On the other hand, chronic ICD (from repeated exposure to a low potential irritant, such as soap) can cause xerosis, desquamation, and fissuring with mild inflammation. Chronic ICD can be difficult to discern clinically from ACD, especially in the wound-healing setting, and care must be taken to improve barrier repair (Table 1).

ACD is a delayed type of hypersensitivity reaction that requires sensitization, which is dependent on the potency of the allergen (e.g., uroshiol and paraphenylenediamine are considered strong sensitizers) and the permeability of the barrier (Fig. 2). In a sensitized individual, exposure may elicit a clinical response in the subsequent days to weeks and can have variable expression of clinical manifestations from eczematous to lichenoid to vesiculobullous reactions. These subsequent re-exposures activate the immune cascade and lead to enhanced reactivity, eventually even with a low dose of causative chemical. After recognition of haptens by T cells, a cascade of inflammatory processes target and eliminate keratinocytes and recruit another wave of T cells. Activation of the innate immune system is also required for the development of ACD. Larger molecules, such as proteins, also involve hormonal immune system while antigen-presenting cells activate the innate immune system. Subsequently, the main immunologic response is related to the interaction of both innate and adaptive immune systems (Mowad et al., 2016).

| Characteristic | Irritant contact dermatitis | Allergic contact dermatitis |
|---------------|-----------------------------|-----------------------------|
| Type          | Direct toxic effect          | Immune mediated             |
| Prior sensitization | No                          | Yes                          |
| Symptoms      | Pain, burning, itching      | Mainly itching              |
| Morphology    | Dermatitis, vesicle, bulla  | Eczematous, vesicles, bulla |
| Borders       | More distinct                | May spread beyond the contact area |
| Postexposure symptoms | Minutes to hours              | Hours to days to weeks      |
| Autosensitization (widespread rash) | No                          | Yes                          |
Most contact allergens are low molecular-weight haptenst that penetrate the skin and couple with host proteins (Gillissen and Goossens, 2016). Dermal dendritic cells present these haptenst to naive T cells, leading to activation of cytokines and generation of CD4 effector T cells (Gillissen and Goossens, 2016; Valois et al., 2015). Although T-helper cells type 1 CD4+ T lymphocytes classically dominate the ACD immunologic response (Kitagaki et al., 1997), other helper cells, specifically T-helper cell type 17, 22 and 29, along with a T-helper cells type 2 response, also play a role (Dhingra et al., 2014; Liu et al., 2014). Additionally, immune polarization patterns have been shown to differ depending on the sensitizing allergen (Dhingra et al., 2014). For example, nickel has been shown to induce a more CD4+ dominant T-cell population, whereas trimethylbenzylin produces a CD8+ dominant T-cell population allergen (Dhingra et al., 2014).

In chronic wounds, the skin barrier is often impaired. Increased levels of tumor necrosis factor alpha and interleukin 1 beta and 6 have been reported in monocytes cultured from patients with venous insufficiency (Signorelli et al., 2000). The immune response in patients with chronic wounds may be altered due to damage to the skin barrier, frequent infections, and associated comorbidities (Baroni et al., 2015). However, multiple studies reported higher rates of CD with prolonged ulcer duration and a link between the majority of evaluations, the allergens are applied in well cham-

**Critical utilization of patch testing for allergic contact dermatitis**

Patch testing is the gold standard to confirm suspected ACD. Patch testing is indicated for patients with acute or chronic pruritic dermatitis where ACD is high on the differential (Fonacier, 2015). Patients with a compromised skin barrier, such as chronic wounds or atopic dermatitis, are particularly susceptible to contact sensitization due to increased permeability of their skin barrier (Fonacier, 2015). As such, among patients with chronic wounds, the threshold to pursue patch testing should be very low.

The American Contact Dermatitis Society routinely (every 2–3 years) presents an evidence-based list of the top 80 allergens in descending order of clinical relevance (Schalock et al., 2017). For the majority of evaluations, the allergens are applied in well chambers to the upper back or inner arm for up to 48 hours. The placement should be documented by photography or a plastic exposure map sheet. When the patches are removed, an initial evaluation (read) is performed and repeated between 72 and 120 hours after patch test placement (Goldenberg et al., 2020). Patients should be instructed to observe the patch test sites even after the conclusion of the test because late-delayed reactions may occur. Table 2 listed the most common allergens in five recent studies.

In some instances, allergens can be urticants in addition to hap-

**Identification of specific allergen in wound-care dressings and cross reactions**

**Hydrogels**

A hydrogel dressing is composed of a hydrophilic polymer that contains carboxymethyl cellulose, an emulsifying agent (e.g., propylene glycol [PG]) and 94% water. Hydrogel dressings can cause both ICD and ACD. ICD can occur due to the high content of water leading to maceration and skin barrier dysfunction (Kohli and Nedorost, 2016). ACD to hydrogel is commonly related to its PG ingredient (Lessmann et al., 2005). PG is a common vehicle in topical medications, cosmetics, and topical corticosteroids. PG exhibits a very low sensitization potential, but it may cause irritant reactions when tested under occlusion (Lessmann et al., 2005).

In a study by Lessmann et al. (2005), the authors reviewed the patch test data of 45,138 patients tested with 2% PG; 2.3% of patients had a positive reaction, 2.4% showed a doubtful follicular or erythematous reaction, and 0.6% had irritant reactions. The backbone of hydrogel can vary and can be a potential cause for ACD as well (Alavi et al., 2016).

Although patch-tests reactions to PG can be questionable, and some even false-positive, sensitization rates to PG may be higher in patients with disrupted skin barrier function (e.g., atopic dermatitis, venous dermatitis, chronic wounds).

**Hydrocolloids**

CD reactions to hydrocolloid dressings have been reported in multiple studies (Valois et al., 2015). The main potential allergen within these dressings is colophony. Although colophony is often
modified with various chemicals, the main allergic components of colophonium are oxidized acids of the abietic acid type (Freise et al., 2008). Colophonium derivatives in hydrocolloid dressings act as tactifying agents (a chemical compound used in adhesives to increase the stickiness of the surface). Although they are similar allergens, they do not cross-react in all cases. Pentaerythritol ester of hydrogenated rosin is a derivative of colophony with the most reported sensitizations. Some patients have positive patch test reactions to pentaerythritol ester of the hydrogenated rosin with no relation to CMC were reported. Hydrofiber dressings also contain CMC. A reaction to hydrofiber dressings (Aquacel) has been reported in some studies (Renner and Wollina, 2002).

Foams

Hydrocellular dressings are made of polyurethane foam. In a study by Valois et al. (2015) of 354 patients, the risk of allergy to polyurethane foam was reported as 1.4%. In a study by Dykes (2007) comparing six wound-care products on 30 disease-free participants, silicone-based soft hydrophilic polyurethane foam dressings had low mean transepidermal water loss values closer to that of normal skin and a better tolerability compared with other dressings.

Antiseptics and antibiotics

For many years, topical antibiotics have been used for the local treatment of abrasions and skin ulcers. The rate of CDA and bacterial resistance raised concern regarding the use of topical antibiotics. Prolonged use of topical antibiotics on damaged skin and under

### Table 2

| Top 20 allergens in patients with leg ulcers in recent studies (2011–2018). |
|---------------------------------|--------------------------|------------------------------------------|
| (Belauksiene et al., 2011) Lithuania; n = 35 | (Valois et al., 2015) France; n = 354 | (Artuz et al., 2016) Turkey; n = 40 | (Erfurt-Berge and Mahler, 2017) Germany/Switzerland; n = 52 | (Rai et al., 2018) India; n = 83 |
| 1. Benzocaine (34.3%) | 1. Balsam of Peru (23.7 %) | 1. Balsam of Peru (30%) | 1. Tertiary-butyl hydroquinone (19.2%) | 1. Wood tar mix (10.4%) |
| 2. Colophonium (20%) | 2. Fragrance mix I (13.3%) | 2. Nickel sulfate (25%) | 2. Amerchol L-101 (17.3%) | 2. Framycetin sulphate (8.7%) |
| 3. Balsam of Peru (20%) | 3. Ialuset cream 45 (12.7%) | 3. Colophonium (22.5%) | 3. Balsam of Peru (13.5%) | 3. Eosin (7.1%) |
| 4. P-phenyldiamine (20%) | 4. Hydrocellular (7.9%) | 4. Fragrance mix II (13.5%) | 4. Cetearyl alcohol (11.5%) | 4. Thimerosal (Merthiolate; 7.1%) |
| 5. Lanolin (17.1%) | 5. Benzalkonium chloride (7%) | 5. Cetearyl alcohol (9.6%) | 5. Lanolin alcohol (9.6%) | 5. 4-chloro-3-cresol (PCMC; 6.6%) |
| 6. Quinolol (8.6%) | 6. Hydrocellular (5.1%) | 6. Nickel sulfur (7.7%) | 6. Cocamidepropyl betaine (7.7%) | 6. Benzalkonium chloride (6.6%) |
| 7. Methyl dibromoglutaronitrile (8.6%) | 7. Oligoacetate (8.6%) | 7. Cetearyl alcohol (5.8%) | 7. Hydrocellular (5.8%) | 7. Propylene glycol (4.9%) |
| 8. Fragrance mix I (5.7%) | 8. Methyl dibromoglutaronitrile (20%) | 8. Thiuram mix (5.8%) | 8. Paraben mix (5.8%) | 8. Triethanolamine (4.4%) |
| 9. Nickle sulfate (5.7%) | 9. Lanolin (4.2%) | 9. Thuriarm mix (2.5%) | 9. Alginates (5.8%) | 9. Chloramphenicol (3.8%) |
| 10. Paraben mix (5.7%) | 10. Cetearyl alcohol (4.5%) | 10. Alginates (5.8%) | 10. Composite mix (5.8%) | 10. Imidazolidinyl urea (4.4%) |
| 11. Sesquiterpene mix (5.7%) | 11. Sodium metabisulfate (4.8%) | 11. Fragrance mix (2.5%) | 11. Propolis (5.8%) | 11. Lidocaine (3.8%) |
| 12. Budesonide (2.9%) | 12. Thiuram mix (2.5%) | 12. Fragrance mix II (2.5%) | 12. Composite mix (5.8%) | 12. Budesonide (2.9%) |
| 13. Formaldehyde (2.9%) | 13. Tetrahydrofuran (2.5%) | 13. Balsam of Peru (20%) | 13. Tertiary-butyl alcohol (3.8%) | 13. Benzocaine (2.9%) |
| 14. Fragrance mix I (2.9%) | 14. Alginates (1.7%) | 14. Tertiary-butyl alcohol (2.9%) | 14. Cetearyl alcohol (5.0%) | 14. Colophonium (2.9%) |
| 15. P-phenyldiamine (2.9%) | 15. Methyl dibromoglutaronitrile (1.7%) | 15. Hydrocellular (5.0%) | 15. Methyldibromo glutaronitrile (2.9%) | 15. Chlorhexidine diglucone (2.7%) |
| 16. Neomycin sulfate (2.9%) | 16. Methyl chloroisothiazolinone (2.5%) | 16. Hydrocellular (5.0%) | 16. Methyldibromo glutaronitrile (2.9%) | 16. Sorbitan monoleate (2.9%) |
| 17. Primin (2.9%) | 17. Alginates (1.7%) | 17. Hydrocellular (5.0%) | 17. Octyl gallate (3.9%) | 17. Budesonide (1.7%) |
| 18. Methylothiozalizolone (2.9%) | 18. Methyl chloroisothiazolinone/ Methylisothiazolinone (2.5%) | 18. Hydrocellular (5.0%) | 18. Butoylated hydroxyanisole (3.8%) | 18. Amoxicillin (1.4%) |
| 19. Paraben mix (2.9%) | 19. Hydrocellular (5.0%) | 19. Hydrocellular (5.0%) | 19. Hydrocellular (5.0%) | 19. Amoxicillin (1.4%) |
| 20. Silver sulfadiazine (1.1%) | 20. Methyl dibromoglutaronitrile (2.5%) | 20. Hydrocellular (5.0%) | 20. Hydrocellular (5.0%) | 20. Silver sulfadiazine (1.1%) |

**Calcium alginates and hydrofiber dressings**

Alginate dressings contain calcium alginates and sometimes carboxymethylcellulose (CMC). There are limited reports of CD to alginate dressings. In a study by Valois et al. (2015), six cases of calcium alginate reaction with no relation to CMC were reported.
occlusion increases the risk of CD. Commonly used topical antibiotics, such as neomycin and polysporin, are on the list of top allergens in most leg ulcer series (Alavi et al., 2016). These reactions can cause considerable morbidity. For example, chloramphenicol, a bacteriostatic broad-spectrum antibiotic, has been reported to involve in causing an extensive prurigo nodularis-like reaction involving body areas beyond where the chloramphenicol-containing ointment was applied (Romita et al., 2019). Therefore, the use of topical antibiotics in the management of chronic wounds is strongly discouraged.

In multiple European studies, lanolin and topical antibiotics are ranked as among the most frequent sensitizers (Barron et al., 2007). Among the antibiotics, neomycin and ciprofloxacin were identified as the most common sensitizers (Valois et al., 2015). Saap et al. (2004) found very similar contact sensitization rates in leg ulcer patients in a North American population.

Antiseptics are commonly used in local wound care. Those commonly used currently are povidone iodine (PVP-I), chlorhexidine, silver octenidine, and polyhexanides (Lachapelle, 2014). In a study by Müller and Kramer (2006), PVP-I 10% was shown to be less aggressive to the stratum corneum compared with PVP-I 7.5% and chlorhexidine. PVP-I has less irritancy in comparison with other antiseptics, such as chlorhexidine (Müller and Kramer 2006). However, skin exposure to PVP-I has been shown to more often cause ICD than ACD (Balato et al., 2011; Lachapelle, 2014).

Large studies have shown a chlorhexidine sensitization rate of 2% after repeated application. The diagnosis is confirmed with patch testing to a 0.5% concentration of chlorhexidine in water (Lachapelle, 2014). Contact urticaria and anaphylactic reactions have been reported with chlorhexidine (Balato et al., 2011). Polyhexamethylene biguanide is a derivative of chlorhexidine that has been used in dressings and can be a potential allergen.

Benzoyl-peroxide sensitivity has been shown commonly in patients with acne and leg ulcers. A positive patch test to 1% benzoyl peroxide was reported from 1.3% to 6.5%, and sensitization to benzoyl peroxides has been reported to range from 9.5% to 14.4% (Pasolini et al., 2004). Therefore, routine use of benzoyl peroxide is not recommended for wound care.

### Natural and alternative treatments

Natural compounds, such as herbs, plant extracts, honey, and propolis, have been used for centuries in certain cultures for wound healing. These products offer the advantage of being more affordable and accessible in some regions, but they come with the disadvantage of limited or contradictory evidence of clinical efficacy, as well as batch-to-batch and regional variations, which can result in unanticipated irritant or allergic reactions. Additionally, many substances frequently used in traditional dressings, such as propolis (a component of honey dressings) are known allergens (Pasolini et al., 2004). Therefore, screening all patients with suspected wound care-related ACD or ICD for use of natural or traditional wound-care therapies is prudent.

Colophony and propolis are both complex plant resins and have been shown to have cross reactions. The cross reaction is unidirectional because patients with a reaction to propolis can show reaction to fragrances and colophony whereas patients with a reaction to fragrances less commonly react to propolis (Shi et al., 2016).

### Treatment of inflammation and dermatitis

The mainstay of ACD and ICD management is to avoid irritants and allergens and then control the inflammation with topical or oral immunosuppressive medication. The use of bland moisturizers and skin barriers devoid of known top sensitizers is recommended to protect the skin, such as Vaseline, pure zinc oxide 40%, and ceramide-rich emollients. A full review of various treatment options for ACD and ICD is beyond the scope of this paper, but a general treatment algorithm is outlined in Table 3.

### Conclusions

The prevalence of chronic leg ulcers and the use of extensive wound-care products, along with the development of CD in this patient population, have increased over the last decade. Clinicians should be cognizant of potential allergens in wound-care products and methods to identify and avoid them. Identifying the causative allergen is the first part in the process, and confirming the sensitization with patch testing is recommended. However, providing wound care free of identified allergens can still be challenging because some wound-care products lack detailed labeling of their true components. Increased clinician, patient, and industry awareness of CD is vital for change.

### Conflicts of interest

None.

### Funding

None.

### Study approval

N/A.

### References

Alavi A, Sibbald GR, Ladizinska B, Saraiya A, Lee KC, Skotnicki-Grant S, et al. Wound-related allergic/irritant contact dermatitis. Adv Skin Wound Care 2016;29(6):278–86.

Artüz F, Yılmaz E, Kültüç Çakmak S, Polat Düzgün A. Contact sensitisation in patients with chronic leg ulcers. Int Wound J 2016;13:1190–2.

Balato A, Balato N, Di Costanzo L, Ayala F. Contact sensitization in the elderly. Clin Dermatol 2011;29:24–30.

Baron A, Piccolo V, Russo T. A possible explanation for the high frequency of contact sensitisation in chronic venous ulcers. Int Wound J 2015;12(3):369–70.

Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: Medical management and beyond. Ann Vasc Surg 2007;21(5):652–62.

Belauskienë A, Valkuviūtë I, Šitkauskienë B, Schmuck A, Uter W. Contact sensitization to the allergens of European baseline series in patients with chronic leg ulcers. Medicina (B Aires) 2011;47(9):480–5.

Bolognia J, Schaffer J, Duncan K, Ko C. Dermatology essentials. Amsterdam, Netherlands: Elsevier; 2014. p. 109–13.

Cook KA, White AA, Shaw DW. Patch testing ingredients of Dermabond and other cyanoacrylate-containing adhesives. Dermatitis 2019;30(5):314–22.

Dhingra N, Shemer A, Correa Da Rosa J, Rozenblit M, Fuentes-Duculan J, Gittler JK, et al. Molecular profiling of contact dermatitis skin identifies allergendependent differences in immune response. J Allergy Clin Immunol 2014;134(2):362–72.

Dykes PJ. The effect of adhesive dressing edges on cutaneous irritancy and skin barrier function. J Wound Care 2007;16(3):97–100.

Erfurt-Berge C, Mahler V. Contact sensitization in patients with lower leg dermatitis, chronic venous insufficiency, and/or chronic leg ulcer: assessment of the clinical relevance of contact allergens. J Investig Allergol Clin Immunol 2017;27(6):378–80.
A. Alavi, A. Goldenberg, S. Jacob et al.

Allergic contact dermatitis in patients with leg ulcers. Contact Dermatitis 1997;36(5):248–91.

Lachapelle JM. A comparison of the irritant and allergenic properties of antiseptics. Lachapelle JM. A comparison of the irritant and allergenic properties of antiseptics. J Invest Dermatol 1998;111(1):9–12.

Kohli N, Nedorost S. Inflamed skin predisposes to sensitization to less potent allergens. J Am Acad Dermatol 2016;75(2):312–317.e1.

Freise J, Kohaus S, Korber A, Hillen U, Kroger K, Grabbie S, et al. Contact sensitization in patients with chronic wounds: Results of a prospective investigation. J Eur Acad Dermatol Venereol 2008;22(10):1203–7.

Valois A, Waton J, Avenel-Audran M, Truchetet F, Collet E, Raison-Peyron N, et al. Contact sensitization to modern dressings: a multicentre study on 354 patients with chronic leg ulcers. Contact Dermatitis 2015;72(2):90–6.

Muller G, Kramer A. Comparative study of in vitro cytotoxicity of povidone-iodine in solution, in ointment or in a liposomal formulation (Repithel®) and selected antiseptics. Dermatology 2006;212(Suppl. 1):91–3.

Fonacier L. A practical guide to patch testing. J Allergy Clin Immunol Pract 2015;3(5):669–75.

Freise J, Kohaus S, Korber A, Hillen U, Kroger K, Grabbie S, et al. Contact sensitization in patients with chronic wounds: Results of a prospective investigation. J Eur Acad Dermatol Venereol 2008;22(10):1203–7.

Gulissen L, Goossens An. Frequency and trends of contact allergy to and iatrogenic contact dermatitis caused by topical drugs over a 25-year period. Contact Dermatitis 2016;75(5):290–302.

Goldenberg A, Ehrlich A, Machler BC, Jacob SE. Patch test clinic start-up: From basics to pearls. Dermatitis 2020;31(5):287–96.

Imbesi S, Minciullo PL, Isola S, Gangemi S. Allergic contact dermatitis: immune system involvement and distinctive clinical cases. Allergol Immunopathol (Madr) 2011;39(6):374–7.

Katsarou-Katsari A, Armenaka M, Katsenis K, Papageorgiou M, Katsambas A, Barellizides A. Contact allergens in patients with leg ulcers. J Eur Acad Dermatol Venereol 1998;11(1):9–12.

Kitagaki H, Ono N, Hayakawa K, Kitazawa T, Watanabe K, Shiohara T. Repeated elicitation of contact hypersensitivity induces a shift in cutaneous cytokine milieu from a T helper cell type 1 to a T helper cell type 2 profile. J Immunol 1997;159(5):2484–91.

Kohli N, Nedorost S. Inflamed skin predisposes to sensitization to less potent allergens. J Am Acad Dermatol 2016;75(2):312–317.e1.

Lachapelle JM. A comparison of the irritant and allergenic properties of antiseptics. J Eur Acad Dermatol Venereol 2006;20(5):426.

Müller G, Kramer A. Comparative study of in vitro cytotoxicity of povidone-iodine solution, in ointment or in a liposomal formulation (Repithel®) and selected antiseptics. Dermatology 2006;212(Suppl. 1):91–3.

Ockenfels HM, Uter W, Lessmann H, Schmich A, Geier J. Patch testing with benzoyl peroxide: reaction profile and interpretation of positive patch test reactions. Contact Dermatitis 2009;61(4):209–16.

Pasolini G, Semenza D, Capezzera R, Sala R, Zane C, Rodella R, et al. Allergic contact dermatitis caused by repeated contact with propolis-enriched honey. Contact Dermatitis 2004;50:322–3.

Pereira TM, Flour M, Goossens A. Allergic contact dermatitis from modified colophonium in wound dressings. Contact Dermatitis 2007;56(1):5–9.

Rai R, Senoy MM, Viswanath V, Sarma N, Majid I, Dogra S. Contact sensitivity in patients with venous leg ulcer: a multi-centric Indian study. Int Wound J 2018;15(4):618–22.

Renner R, Wollina U. Contact sensitization in patients with leg ulcers and/or eczema: comparison between centers. Int J Low Extrem Wounds 2002;1(4):251–5.

Romita P, Stingeni L, Hansel K, Ettorre G, Bosco A, Ambrogio F, et al. Allergic contact dermatitis caused by chloramphenicol with prurigo nodularis-like spreading. Contact Dermatitis 2019;80:251–2.

Saap LJ, Fahim S, Arsenault E, Pedvis-Lefick A. Contact sensitivity in patients with leg ulcers. J Am Acad Dermatol 2004;140:1241–6.

Schalock PC, Dunning CA, Nedorost S, Brod B, Warshaw E, Mowad C. American contact dermatitis society core allergen series: 2017 update. Dermatitis 2017;28(2):141–3.

Shah JB. The history of wound care. J Am Col Certif Wound Spec 2011;3(3):65–6.

Shi Y, Nedorost S, Scheman L, Scheman A. Propolis, colophony, and fragrance cross-reactions in persons with leg ulcers: a Canadian study in contact sensitization. J Int Wound J 2012;9(4):251–5.

Signorelli SS, Malaponte MG, Di PL, Costa MP, Pennisi G, Mazzarino MC. Venous stasis causes release of interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) by monocyte-macrophage. Clin Hemorheol Microcirc 2000;22(4):311–6.

Smart V, Alavi A, Couotts P, Fierheller M, Coelho S, Linn Holness D, et al. Contact allergens in persons with leg ulcers: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. Br J Dermatol 2004;150(5):929–35.

Saap LJ, Fahim S, Arsenault E, Pedvis-Lefick A. Contact sensitivity in patients with leg ulcers. J Am Acad Dermatol 2004;140:1241–6.

Schalock PC, Dunning CA, Nedorost S, Brod B, Warshaw E, Mowad C. American contact dermatitis society core allergen series: 2017 update. Dermatitis 2017;28(2):141–3.

Shah JB. The history of wound care. J Am Col Certif Wound Spec 2011;3(3):65–6.

Shi Y, Nedorost S, Scheman L, Scheman A. Propolis, colophony, and fragrance cross-reactions in persons with leg ulcers: a Canadian study in contact sensitization. J Int Wound J 2012;9(4):251–5.

Signorelli SS, Malaponte MG, Di PL, Costa MP, Pennisi G, Mazzarino MC. Venous stasis causes release of interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) by monocyte-macrophage. Clin Hemorheol Microcirc 2000;22(4):311–6.

Smart V, Alavi A, Couotts P, Fierheller M, Coelho S, Linn Holness D, et al. Contact allergens in persons with leg ulcers: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. Br J Dermatol 2004;150(5):929–35.

Saap LJ, Fahim S, Arsenault E, Pedvis-Lefick A. Contact sensitivity in patients with leg ulcers. J Am Acad Dermatol 2004;140:1241–6.

Schalock PC, Dunning CA, Nedorost S, Brod B, Warshaw E, Mowad C. American contact dermatitis society core allergen series: 2017 update. Dermatitis 2017;28(2):141–3.

Shah JB. The history of wound care. J Am Col Certif Wound Spec 2011;3(3):65–6.

Shi Y, Nedorost S, Scheman L, Scheman A. Propolis, colophony, and fragrance cross-reactions in persons with leg ulcers: a Canadian study in contact sensitization. J Int Wound J 2012;9(4):251–5.

Signorelli SS, Malaponte MG, Di PL, Costa MP, Pennisi G, Mazzarino MC. Venous stasis causes release of interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) by monocyte-macrophage. Clin Hemorheol Microcirc 2000;22(4):311–6.

Smart V, Alavi A, Couotts P, Fierheller M, Coelho S, Linn Holness D, et al. Contact allergens in persons with leg ulcers: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. Br J Dermatol 2004;150(5):929–35.

Saap LJ, Fahim S, Arsenault E, Pedvis-Lefick A. Contact sensitivity in patients with leg ulcers. J Am Acad Dermatol 2004;140:1241–6.

Schalock PC, Dunning CA, Nedorost S, Brod B, Warshaw E, Mowad C. American contact dermatitis society core allergen series: 2017 update. Dermatitis 2017;28(2):141–3.