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Review

Contact dermatitis: An important consideration in leg ulcers

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ABSTRACT

The prevalence of chronic wounds is increasing with the aging population, with 1% to 2% of the worldwide 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.

Contents

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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 (Marasović and Vuksić, 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 (Bolognia 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).

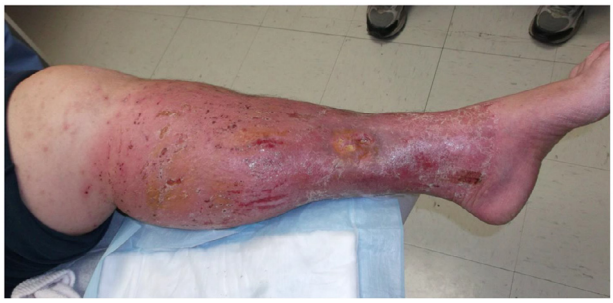

Fig. 1. Irritant contact dermatitis due to excessive drainage from the ulcer under the compression therapy.

Table 1
Characteristics of acute allergic versus acute irritant contact dermatitis.

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

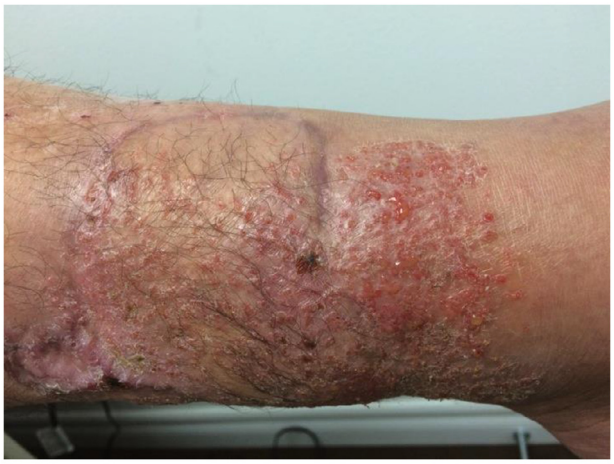

Fig. 2. Allergic contact dermatitis due to use of polysporin cream on the wound area.

Most contact allergens are low molecular-weight haptens that penetrate the skin and couple with host proteins (Gilissen and Goossens, 2016). Dermal dendritic cells present these haptens to naïve T cells, leading to activation of cytokines and generation of CD4 effector T cells (Gilissen 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 trinitrophenyl 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 prevalence of CD and delayed wound-healing time. Table 1 outlines the differences in both ACD and ICD.

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 haptens, such as bacitracin and benzoates. In these evaluations, the patches may be applied in duplicate, and the first series of patches are removed and evaluated at 30 minutes. The duplicate is left on for the full 48 hours. If there is concern for a high false-negative rate, the allergens may also be applied in duplicate (one on the back and one 1 cm from the dermatitis area of the chronic wound; i.e., lanolin, paraben; practice experience observation). Checking for delayed reactions and judiciously considering the impact of doubtful reactions is important because these may still be of high clinical relevance (Mowad et al., 2016).

The detection of allergens in modern dressings is challenging due to a lack of standard patch-test series for wound-care product ingredients. Thus, considering patch testing with 1 cm square pieces of the patient's own wound-care supplies directly on the skin on the back with a reading after 48 hours, along with a standard series of allergens, is recommended. However, with the use of this open-application test technique, the risk of false-negative reactions is high because the dressings are applied to normal skin. Thus, some providers gently abrade the skin prior to the placement of the dressings to simulate injured or nonhealing skin (Cook et al., 2019).

The top 15 high-risk allergens within the chronic wound population include nickel, cobalt, neomycin, bacitracin, balsam of Peru, fragrance mix I and II, colophony, methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, paraben mix, lanolin/amerchol, propylene glycol, benzylkonium chloride, cocamidopropylbetaine, formaldehyde, quaternium 15, imidazolidinyl urea, diazolidinyl urea, bronopol, clioquinol, chlorhexidine, and class A and B corticosteroids.

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 20% 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

Table 2
Top 20 allergens in patients with leg ulcers in recent studies (2011–2018).

(Beliauskiene et al., 2011) Lithuania; n = 35	(Valois et al., 2015) France; n = 354	(Artüz 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 (50%)	1. Tertiary-butyl hydroquinone (19.2%)	1. Wood tar mix (10.4%)
2. Colophonium (20%)	2. Fragrance mix I (13.3%)	2. Nickle 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. Benzocaine (20%)	4. Fragrance mix II (13.5%)	4. Thimerosal (Merthiolate; 7.1%)
5. Lanolin (17.1%)	5. Benzalkanium chloride (7%)	5. Fragrance mix II (12.5%)	5. Cetearyl alcohol (11.5%)	5. 4-chloro-3-cresol (PCMC; 6.6%)
6. Quinolol (8.6%)	6. Amercol L 101 (5.4%)	6. Thiuram mix (2.5%)	6. Lanolin alcohol (9.6%)	6. Benzalkonium chloride (6.6%)
7. Methyl dibromo glutaronitrile (8.6%)	7. Hydrocolloid (5.1%)	7. K dichromate (2.5%)	7. Nickel sulfate (7.7%)	7. Propylene glycol (4.9%)
8. Fragrance mix I (5.7%)	8. Colophonium (4%)	8. Paraben mix (2.5%)	8. Cocamidopropyl betaine (7.7%)	8. Triethanolamine (4.4%)
9. Nickle sulfate (5.7%)	9. Lanolin (4.2%)		9. Colophony (5.8%)	9. Chloramphenicol (3.8%)
10. Paraben mix (5.7%)	10. Cetearyl alcohol (4.5%)		10. Fragrance mix I (5.8%)	10. Imidazolidinyl urea (Germall 115; 3.8%)
11. Sesquiterpene mix (5.7%)	11. Sodium metabisulfate (4.8%)		11. Propolis (5.8%)	11. Nitrofurazone (3.3%)
12. Budesonide (2.9%)	12. Thiuram mix (2.3%)		12. Composite mix (5.8%)	12. Phenyl mercuric acetate (3.3%)
13. Formaldehyde (2.9%)	13. Alginates (1.7%)		13. Propylene glycol (5.8%)	13. Propolis (3.3%)
14. Fragrance mix I (2.9%)	14. Methyl dibromo glutaronitrile (1.7%)		14. Benzophenone-4 (sulisobenzone; 5.8%)	14. Amerchol L 101 (2.7%)
15. P-phenyldiamine (2.9%)	15. P-phenyldiamine (1.4%)		15. P-tertiary-butylphenol formaldehyde resin (3.8%)	15. Chlorhexidine digluconate (2.7%)
16. Neomycin sulfate (2.9%)	16. Propylene glycol (1.4%)		16. Methyldibromo glutaronitrile (3.8%)	16. Sorbitan monoleate (span 80) (2.7%)
17. Primin (2.9%)	17. Paraben mix (1.4%)		17. Octyl gallate (3.8%)	17. Bacitracin (2.2%)
18. Methyisothiazolinone (2.9%)	18. Methylchloroisothiazolinone/ Methylisothiazolinone (1.4%)		18. Butylated hydroxyanisole (3.8%)	18. Cetearyl alcohol (2.2%)
	19. Hydrofiber (1.4%)		19. Paraben mix (1.9%)	19. Diazolidinyl urea (Germall II; 2.2%)
	20. Silver sulfadiazine (1.1%)		20. Bufexamac (1.9%)	20. Fusidic acid sodium salt (2.2%)
			21. Polyethylene glycol ointment (DAB 8; 1.9%)	21. Sorbitan sesquioleate (2.2%)
				22. 2,6-ditert-butyl-4-cresol (1.6%)
				23. Budesonide (1.6%)
				24. Sorbic acid (1.6%)
				25. Benzoyl peroxide (1.1%)
				26. Chloroacetamide (1.1%)

modified with various chemicals, the main allergenic 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. Pentaerythriolester 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 without a cross-reaction to colophonium (Pereira et al., 2007). These patients react only to a modified colophonium derivative. Thus, in patients where ACD from hydrocolloid dressings is strongly suspected and colophonium tests negatively, patch testing to modified colophonium derivatives should be performed.

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. Hydrofiber dressings also contain CMC. A reaction to hydrofiber (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 CD and bacterial resistance raised concern regarding the use of topical antibiotics. Prolonged use of topical antibiotics on damaged skin and under

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 cause 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 clioquinol 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% (Foti et al., 2015; Ockenfels et al., 2009). ICD has also been reported with benzoyl peroxide (Renner and Wollina, 2002). 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.

Table 3
Treatment algorithm.

a) Detection of inciting agent (irritant by history; allergy by patch test)
b) Avoidance of allergen or irritant
c) Promote barrier repair (acidification, emollients with ceramides)
d) Allergic, then apply topical steroids and avoidance protocol

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

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