

Shoe Allergic Contact Dermatitis

Erin Matthys, BS,* Amir Zahir, MD,† and Alison Ehrlich, MD, MHS‡

Foot dermatitis is a widespread condition, affecting men and women of all ages. Because of the location, this condition may present as a debilitating problem to those who have it. Allergic contact dermatitis involving the feet is frequently due to shoes or socks. The allergens that cause shoe dermatitis can be found in any constituent of footwear, including rubber, adhesives, leather, dyes, metals, and medicaments. The goal of treatment is to identify and minimize contact with the offending allergen(s). The lack of product information released from shoe manufacturers and the continually changing trends in footwear present a challenge in treating this condition. The aim of this study is to review the current literature on allergic contact shoe dermatitis; clinical presentation, allergens, patch testing, and management will be discussed. PubMed and MEDLINE databases were used for the search, with a focus on literature updates from the last 15 years.

The prevalence of shoe allergic contact dermatitis (ACD) varies from 1.5% to 24.2% of patch-tested patients.^{1–4} The problem is found in both males and females, although there is some discrepancy in regards to which group it occurs in most commonly. Saha et al³ found a slightly higher prevalence among males, which they attributed to more occlusive male footwear, prolonged use of footwear in males, and/or absence of the responsible allergens in the testing series for females. In contrast, Rani et al⁴ found the female-to-male ratio to be 4.7:1. This was attributed to the greater variation in footwear in females and an increased awareness of changes in their skin compared with males.⁴

When facing persistent foot eczema, it is necessary to consider other conditions that may have similar clinical presentations. Irritant dermatitis, dyshidrosis, psoriasis, tinea pedis, lichen planus, juvenile plantar dermatosis, and id reactions are all included in the differential of ACD.⁵ Irritant contact dermatitis may arise from the rubbing of footwear against the feet or from contact with irritants, such as detergents, soaps, cement, or topical medications. In contrast to ACD, there is no immunological mechanism involved in this response.⁶ Psoriasis should also not be overlooked. In a 5-year retrospective study of 70 patients suspected of ACD of the feet, only

23 received a final diagnosis of ACD; 30 patients were determined to have psoriasis.⁵

From an epidemiologic standpoint, shoe ACD has been difficult to characterize because of variation in the series of allergens tested, differing shoe manufacturing processes, and changing trends in footwear across time and regions of the world.^{7,8} Despite and owing to this challenge, shoe dermatitis calls for further sustained research and better understanding because it impacts so many people.

Allergic contact dermatitis is a form of delayed type hypersensitivity reaction caused by exposure to exogenous chemical and physical agents. It can occur in acute, subacute, or chronic forms. The acute form is distinguished by the presence of erythema and edema, followed by the formation of tiny vesicles and crusted, weeping lesions. In chronic contact dermatitis, the skin may become lichenified, fissured, or pigmented; episodes of oozing and crusting may arise. Shoe allergy is often indicated by the presence of erythema, papules, vesicles, oozing, scaling, or crusting at the site of contact. Spreading of the reaction may also occur. Allergic contact dermatitis of the feet is typically bilateral and symmetrical, although it may also present unilaterally. Pruritus, burning, and pain are the most commonly reported symptoms.⁴ The particular environment within shoes, in conjunction with allergens, contributes to the susceptibility of feet to ACD.⁹ Landeck et al⁸ found the occlusive, moist environment of shoes to be the cofactor that had the largest negative impact on foot dermatitis, followed by chronic venous insufficiency, friction, and heat. Although any region of the foot can be affected, the dorsum of the foot is involved most frequently because of its greater surface area, thin stratum corneum, and sustained interaction with the upper portion of the shoe.

Foot dermatitis may often arise among particular occupational groups such as factory workers and military personnel because of the heavy occlusive footwear used in these occupations. Within a group of soldiers who were patch tested for dermatitis of the lower limbs, 27 of 31 showed a positive reaction to 1 or more allergens

From the *Department of Medicine, Mercy Medical Center, Baltimore, MD; †School of Medicine and Health Sciences, and ‡Department of Dermatology, Medical Faculty Associates, George Washington University, Washington, DC.

Address reprint requests to Alison Ehrlich, MD, MHS, Department of Dermatology, Medical Faculty Associates, George Washington University, 2150 Pennsylvania Ave, NW, Washington, DC, 20037. E-mail: aehrich@mfa.gwu.edu.

Funding sources: Dr Amir Zahir was a research fellow at the George Washington University, Medical Faculty Associates, whose fellowship was partially supported by the Abbott and Janssen Biotech.

The authors have no conflicts of interests to declare.

DOI: 10.1097/DER.0000000000000049

© 2014 American Contact Dermatitis Society. All Rights Reserved.

from direct testing with parts of their military boots.¹⁰ Among the nonmilitary population, Lazzarini et al⁶ found occupational activity to be the contributing cause for 15% of patients with foot dermatitis. Warshaw et al⁷ reported a lower percentage, with only 2.6% of positive patch test results for foot dermatitis considered to be occupationally relevant.

Chemicals used in manufacturing shoes, socks, or stockings are often the contributing cause of ACD of the feet. Rubber, adhesives, leather, synthetic polymers, and dyes are all known sources of allergens.^{8,9}

ALLERGENS

Rubber and Rubber Additives

Rubber allergy from shoes may arise from the elastic found in the uppers of shoes, the rubber adhesives in shoe linings, or rubber innersoles.¹ Rubber exists in both natural and synthetic form, and shoe rubbers may contain a mixture of both. A number of rubber additives, including thiurams, benzothiazoles, carbamates, *para*-phenylenediamine derivatives, thioureas, and resin components, have been identified as allergens in shoe testing series.^{8,9} Freeman et al¹ found rubber chemicals to be the most common allergen, with 43% of patients reacting positively to either mercapto mix, mercaptobenzothiazole, or thiuram mix. In a 2001–2004 North American Contact Dermatitis Group study, rubber chemicals were the most common shoe allergens when combined as a group, which included carba mix, thiuram mix, mercaptobenzothiazole, mercapto mix, mixed dialkyl ureas, and black rubber mix.⁷ Similarly, in a Brazilian study, rubber additives accounted for 27% of positive patch test results for foot dermatitis; the most frequent causative allergen was the mercapto group, followed by thiuram mix, *para*-phenylenediamine mix, and carba mix.⁶

Thioureas, chemical accelerators used in the production of neoprene and foam rubber, are a common cause of contact dermatitis.^{11,12} A Finnish study found that 59 of 15,100 patients had a positive patch test reaction to thiourea mix. Of these 59 patients, 33 were tested with individual rubber chemicals, of which 24 (73%) reacted positively to diethylthiourea. Diphenylthiourea, dibutylthiourea, diphenylguanidine, carbamates, mercaptobenzothiazole, and diaminodiphenylmethane also elicited positive patch test reactions.¹³ Friis et al¹¹ reported a patient who developed ACD of the feet from a pair of neoprene running shoes; the patient later tested positive to diethylthiourea. His shoes were found to have a diethylthiourea concentration of 192 to 251 ppm.¹¹ 4,4-Dithiodimorpholine (DTDM), another type of rubber accelerator which may be found in rubber components of shoes, is considered to be an allergen often missed by commercial patch testing kits, but its relevance is debated. DTDM caused the most positive and relevant reactions in patients with ACD due to shoes in a study assessing the etiology of allergic-appearing dermatitis.¹⁴ In addition, it was 1 of the most frequent allergens that caused ACD to components of shoes in a 5-year retrospective study of allergic-appearing foot dermatitis.⁵ Despite these findings, there are reports that it has high irritancy and low relevancy rates.⁷

Black or gray rubber is a common cause of occupational dermatitis, and it is screened by patch testing for *para*-phenylenediamine-related antioxidants (*N*-isopropyl-*N*-phenyl-4-phenylenediamine, *N*-cyclohexyl-*N*-phenyl-4-phenylenediamine, and *N*, *N*-diphenyl-4-phenylenediamine).¹⁵ A statistically significant association has been found between sensitization to *para*-phenylenediamine and 4,4'-diaminodiphenylmethane (DDM), an aromatic diamine used in the production of rubber, plastics, diisocyanates, dyes, and adhesives. In a specific study of DDM-sensitized patients, the relative risk of reacting to *para*-phenylenediamine was determined to be 24.¹⁶ DDM has recently been associated with shoe-related contact allergy in cases involving Asian-manufactured shoes. In this study, 3 patients with suspected shoe contact dermatitis were patch tested with the European baseline series and a shoe and diisocyanate series; all 3 only reacted positively to DDM.¹⁷ An additional rubber additive sensitizer to test for is hydroquinone monobenzylether, a rubber antioxidant and depigmenting agent.³ Among those not already mentioned, cyclohexylthiophthalimide was found to be a common rubber allergen in an 8-year retrospective review of patch testing with rubber allergens.¹⁸

Castanedo-Tardan et al¹⁹ discussed a case study of a child with dermatitis on the dorsal and ventral feet surfaces who admittedly only wore tennis shoes and Crocs. Patch testing was reactive for black rubber mix, thiuram mix, carba mix, and disperse blue 106, but ultimately, the patient had the strongest reaction to a sample of his Crocs footwear. Unfortunately, attempts to determine which chemicals are used in the manufacturing of Crocs were met without success; however, the patient's dermatitis did resolve when he discontinued wearing those shoes. This case emphasizes part of the challenge in identifying the precise allergen causing shoe ACD. However, it also draws attention to the importance of patch testing with direct shoe samples, which will be discussed further.¹⁹

Adhesives

Adhesive sensitivity is a cause of shoe dermatitis, although there is variation in the literature in regards to its frequency. *p*-tertiary-Butylphenol formaldehyde resin (PTBFR) is used in shoe production as a binder in adhesive formulations.²⁰ In a retrospective North American study of 109 patients with ACD of the feet, PTBFR was reported to be the most common shoe allergen; it accounted for 24.7% of positive patch testing results.⁷ Similarly, Rani et al⁴ found glues as a group, particularly PTBFR, to be the leading allergens in a Pakistani study of 119 patients suspected of having shoe dermatitis. However, other studies have reported a less frequent allergy to PTBFR. Throughout a 10-year period of patch testing, Holden and Gawkrödger²¹ reported a positive reaction to PTBFR in only 1 of 230 patients tested. Lazzarini et al⁶ reported no positive patch test reactions to PTBFR in their study of 53 patients evaluated for foot dermatitis. Furthermore, Shackelford and Belsito⁵ reported that of 704 patients with suspected ACD, 13 had a PTBFR allergy, yet only 3 patients had ACD due to PTBFR in shoes. The latter diagnosis was determined by characteristic dermatitis of the feet, a positive

patch test result to the relevant piece of footwear, and resolution of the dermatitis upon avoidance of the allergen.

Colophony, a sap from pine or spruce trees that is used in natural rubber latex cement, is a common sensitizer in foot dermatitis.^{3,4} Lazzarini et al⁶ reported positive patch test reactions to colophony in 5.5% of patients, whereas Freeman¹ reported a slightly higher frequency at 9%. Abietic acid is a major component of colophony. The oxidation products of this resin acid have been shown to be ACD sensitizers, and abietic acid is included in some footwear testing series.²² Other known shoe glue allergens include dodecylmercaptan and epoxy resins.⁴ Epoxy resins may be produced by polymerizing the diglycidyl ether of bisphenol A (DGEBA); a small percentage is also produced through the polymerization of the diglycidyl ether of bisphenol F (DGEBF).²³ Both DGEBA and DGEBF have been implicated as allergens in foot dermatitis. Srinivas et al²⁴ reported 2 patients presenting with foot dermatitis after wearing plastic flip flops; upon patch testing with various plastic and shoe glue allergens, both patients developed an erythematous vesicular reaction to bisphenol A (1% petrolatum [pet]).

Plasticizers have also been implicated in ACD of the feet. Benzoyl peroxide is a glue catalyst and plasticizer that has been used in the treatment of leather with synthetic resins. It is often included in patch testing series and is a recognized foot dermatitis allergen.²⁵ Nardelli et al²⁵ reported 11 positive patch test results to benzoyl peroxide in their 13-year retrospective study in Belgium. In addition, Vidović et al²⁶ discussed the case of workers in a factory producing shoes from polyvinyl chloride who became sensitized to dibutylphthalate, a plasticizer.

Tanning Agent Allergens

Chromium salts are frequently used to tan leather footwear. Trivalent salts, such as chromic acid, chromic sulfate, and chrome trichloride, are more frequently used for tanning and act by binding to the collagen and stabilizing the leather. The Cr(III) salts may oxidize to hexavalent chromium [Cr(VI)] during the tanning process. The hexavalent salts, including potassium dichromate, do not bind well to proteins and are more often found in free and unbound form. As a result of their ability to leach out of leather and because of their increased bioavailability, hexavalent salts are more potent contact allergens and have proven to be more consistent for patch testing use.²⁷ In a study assessing the risk of chromium allergy from leather footwear, chromium was identified in 95% of 60 pairs of leather shoe wear, ranging from men's, women's, and children's items.²⁸ Saha et al³ found potassium chromate to be the most common sensitizer in their study. Warshaw et al⁷ found hexavalent potassium dichromate to be the second most common shoe allergen, accounting for 17.5% of positive patch test reactions. Rani et al⁴ also reported a high positive reaction to leather allergens, particularly potassium dichromate (16.8%), formaldehyde (5.9%), and 2-n-octyl-4-isothiazolin-3-one (3.7%). Chowdhuri et al² found potassium dichromate (45.8%) to be the most common allergen in foot dermatitis; this was believed to be

due to the minimal use of chrome-free leather in India because of its high cost and lack of availability.

Although Cr(III) is thought to have low allergenic potency, Hansen et al²⁷ showed that both Cr(III) and Cr(VI) are capable of eliciting ACD reactions at low concentrations within the same patient. In this study of 2211 patients suspected of ACD of the feet, 71 patients had a positive reaction to potassium dichromate [Cr(VI)], and of those, 31 reacted positively to chromium trichloride [Cr(III)]. Furthermore, patients who reacted positively to both Cr(VI) and Cr(III) had an increased risk of foot dermatitis compared with patients who only reacted positively to Cr(VI). Hansen et al²⁹ recommend testing for both oxidation states in cases of suspected chromium-induced leather dermatitis. Thyssen et al³⁰ described a recent case report of a patient with potassium dichromate allergy who continued to react to "chromium-free" footwear. When the chromium-free footwear was analyzed for chromium content, chromium was verified with x-ray fluorescent spectroscopy, but spot testing result to detect Cr(VI) was negative. The authors believe that Cr(III) was the cause of her persistent dermatitis.³⁰

Vegetable tannins are used to tan leather in some countries and are often used as a substitute for individuals with chromate allergy. The tannins consist of plant or fruit extracts, including quebracho, wattle bark, myrobalan, mimosa, and chestnut extracts.^{3,31} Although these tannins have been used as an alternative for individuals with chromate allergy, they have also been reported to be sensitizers in cases of foot dermatitis.¹ Formaldehyde and glutaraldehyde may also be used in the tanning process, but these are less common sources of leather allergens.⁹

Dimethyl Fumarate

Dimethyl fumarate (DMF), the methyl ester form of fumaric acid, was first identified as a potent contact sensitizer during a contact dermatitis outbreak that occurred because of its use in Chinese-manufactured furniture.^{32,33} Dimethyl fumarate inhibits the growth of mold; it has been used to protect leather during storage and transport.³⁴ Numerous studies have documented DMF as an allergen in shoe dermatitis. Dimethyl fumarate is commonly placed in sachets within shoe boxes and has been found to impregnate and remain within footwear for long periods.³⁵ Giménez-Arnau et al³⁶ studied 17 patients with contact dermatitis of the feet due to DMF. All 15 adults in the study developed a delayed sensitization confirmed by positive patch test results to DMF less than or equal to 0.1% in pet. Chemical analysis verified the presence of DMF in the shoes of all patients that showed a positive reaction to their own shoe sample.³⁶ In another study, Silvestre et al³⁷ found that patients with shoe dermatitis who had positive patch test results for DMF were likely to present with erythema primarily involving the dorsum of toes and feet (59%), followed by the entire foot (38.6%) and the bottom third of the leg (22.7%). Dimethyl fumarate was identified in all shoe samples through the use of gas chromatography/mass spectrometry in this study.³⁷ In another study, the concentration of DMF in various components of shoes was found to correlate with the localization of lesions.³¹

D'Erme et al³⁴ reported a unique case in which a patient developed headache, fever, and malaise in addition to severe eczema on the dorsum and soles of her feet after contact with DMF in a recently purchased pair of shoes manufactured in China. Vesicles were found at the site of shoe contact. Upon chemical analysis, a concentration of 740 mg/kg of DMF was found in the shoes.³⁴ The European Commission has banned items containing more than a concentration of 0.1 mg/kg from the European market since March 2009. D'Erme and colleagues³⁴ advocate stricter widespread regulation to eliminate DMF exposure.

Dyes

An allergy to dyes may be missed due to a lack of the necessary chemicals for testing.⁹ Rani et al⁴ found dyes, particularly *para*-phenylenediamine and 4-aminoazobenzene, to be the cause of 7.6% of positive patch test results in their study. *Para*-phenylenediamine is a common dye allergen because of the preference for black coloring in shoes and socks.² Disperse orange 3, acid yellow 36, disperse red 1, and disperse blue 106/124 mix have also been shown to cause shoe allergy.^{3,23}

Metals

Many metals are skin sensitizers; however, nickel, cobalt, chromium, and mercury ions/compounds are most commonly involved in ACD of the feet. There is variation among the literature in regards to the relevance of nickel as a foot dermatitis allergen. Holden and Gawkrödger²¹ suggest that nickel is not a pertinent concern unless there is an obvious source, such as a metal buckle. In contrast, Lazzarini et al⁶ reported nickel sulfate to be an important allergen. Onder and colleagues⁹ presented the case of a patient who developed a reaction to metal buttons on her slippers; patch testing showed a positive reaction to nickel sulfate. Rani et al⁴ reported that 22.7% of patients patch tested for shoe dermatitis were sensitive to nickel sulfate. Of those, only 18% showed clinical relevance.⁴ Cobalt dichloride has also been determined to be a cause of shoe allergy.⁸ It was 1 of the most frequent causes of allergy in an Indian study by Chowdhuri et al² thought to be due to the increasing use of cobalt in shoe buckles and eyelets. Goossens and colleagues³⁸ described the case of a patient who had concomitant allergic reactions to both nickel and cobalt within the same pair of plastic shoes. Nickel and cobalt compounds may be used in dyes and pigments, which likely contributed to the concomitant reaction in this particular patient. Furthermore, Koch and Nickolaus³⁹ reported a young boy who developed severe ACD, and eventually mercury exanthema, after wearing polyvinyl chloride boots. Patch test results for inorganic and organic mercury compounds were positive.

Socks and Hosiery

In a study of textile allergens that resulted in ACD, Opie et al⁴⁰ found basic red 46 to be the most common cause of dye allergy,

with acrylic-blend men's work socks being the common source. In a study by Slodownik et al⁴¹ that explored ACD of the feet and other regions of the body, a number of textile dyes were implicated as allergens (Table 1).

Rubber within socks has also been implicated as an allergen in shoe dermatitis. N, N-Dibenzyl carbamyl chloride is the responsible allergen that is formed when a rubber accelerator called zinc dibenzylthiocarbamate reacts with sodium hypochlorite (bleach), causing a reaction known as the bleached rubber syndrome. Jordan et al⁴² originally recognized this occurrence with undergarment elastic that had been bleached, and they were able to identify the compounds in the reaction mixture by gas chromatography/mass spectroscopy. In bleached rubber syndrome, patients will show a reaction to the bleached clothing but have no reaction to the identical, nonbleached clothing.⁴³ Another rubber antigen, mercaptoben-zothiazole, can remain within cotton socks despite washing and boiling, contributing to cases of persistent dermatitis.⁴⁴

Nylon stockings may also present as a source of ACD due to either the dye used or the fiber itself. In earlier reports, patch testing suggested that the finish and dyes were the source of allergen; however, a number of studies have implicated the synthetic fibers. The number of cases of "nylon dermatitis" due to fiber has declined since the mid 1900s likely because of improvements in fiber production that have led to the use of lower molecular weight residues within the fiber.⁴⁵ In a more recent study, disperse yellow 3, disperse red 1, disperse blue 3, and disperse orange 3 used in women's stockings were shown to cause ACD.⁴⁶ Imbeau and Reed⁴⁷ presented a case of a patient who reacted positively to disperse yellow 3 and disperse red 1 dyes found within stockings; (s)he did not react to the raw nylon or nylon finish. Perez-Crespo et al⁴⁶ recommend patch testing patients with a textile series as needed in addition to the shoe tray.

TABLE 1. Textile Dye Allergens⁴¹

Disperse orange 3 (1.0 pet.)
Disperse red 1 (1.0 pet.)
Disperse red 17 (1.0 pet.)
Disperse blue 153 (1.0 pet.)
Disperse blue 3 (1.0 pet.)
Disperse blue 35 (1.0 pet.)
Disperse blue 106 (1.0 pet.)
Disperse blue 85 (1.0 pet.)
Disperse orange 1 (1.0 pet.)
Disperse brown 1 (1.0 pet.)
Disperse yellow 9 (1.0 pet.)
Disperse blue 124 (1.0 pet.)
Basic red 46 (1.0 pet.)
Reactive blue 21 (5.0 pet.)
Reactive red 123 (5.0 pet.)
Reactive red 238 (5.0 pet.)
Direct orange 34 (5.0 pet.)
Disperse blue 106/124 mix (1.0 each in pet.)

pet., petrolatum.

PATCH TESTING

Practical Considerations

Testing on disease-free skin is essential for identifying the offending allergen; this may include testing with chemicals from the standard series, an expanded shoe series, and/or pieces of the patient's shoe.^{1,4} An understanding of shoe construction, particularly concerning the chemical components that go into each part of the shoe, may be advantageous as an initial approach in determining the culprit allergen. Patch testing with the patient's shoe itself should be performed using pieces of the shoe that are in contact with the reactive skin. Epstein supports the importance of patch testing with shoes, and to minimize false negatives, he urges that the following techniques be used: test all footwear, use the upper back as a test site, and use materials of at least 1 cm² and less than 2 mm thick.⁴⁸

Particular caution should be taken to avoid obtaining false-positive irritant pressure reactions; thus, the shoe pieces being tested should be thin.¹ Table 2 provides a list of relevant patch testing allergens within the TRUE Series, Chemotechnique Diagnostic shoe series, and allergEAZE shoe panel.

Unknown allergens may also be detected by further chemical analysis. Bruze et al⁴⁹ discussed the technique of using ultrasonic bath to extract chemicals from materials for further patch testing. In this technique, the material is placed in a solvent suitable for the particular sensitizer within a glass jar, which is then placed in an ultrasonic bath. After this, the original material is removed, and the solvent is evaporated. A solvent is then added to the remaining residue in the jar, and together this forms the stock solution to be used for patch testing. Bruze et al⁴⁹ have found ultrasonic bath extraction to be an advantageous technique to use when there are

TABLE 2. Patch Testing Series for Shoe Dermatitis

TRUE Series Potentially Relevant Allergens	Chemotechnique Diagnostic Shoe Series	allergEAZE Footwear Grouping
Panel 1.2	IPPD (0.1% pet.)	1,3-Diphenylguanidine (1.0% pet.)
Nickel sulfate	Glutaral (0.2% pet.)	MBT (2.0% pet.)
Wool alcohols	Disperse orange 3 (1% pet.)	4,4'-Diaminodiphenyl methane (0.5%)
Neomycin sulfate	Acid yellow 36 (1% pet.)	4-Aminoazobenzene (1.0% pet.)
Potassium dichromate	Hydroquinone monobenzylether (1% pet.)	4-Phenylenediamine base (1.0% pet.)
Fragrance mix	Thiuram mix (1% pet.)	4- <i>tert</i> -Butylphenol formaldehyde resin (1.0% pet.)
Colophony	Tetramethylthiuram monosulfide (0.25)	Abietic acid (10.0% pet.)
Paraben mix	Teramethylthiuram disulfide (0.25)	Benzoyl peroxide (1.0% pet.)
Balsam of Peru	Tetramethylthiuram disulfide (0.25)	Black rubber mix – IPPD (0.5% pet.)
Cobalt dichloride	Dipentamethylenethiuram disulfide (0.25)	Carba mix (3.0% pet.)
Panel 2.2	Potassium dichromate (0.5% pet.)	Cobalt(II) sulfate (2.5% pet.)
<i>p</i> - <i>tert</i> -Butylphenol formaldehyde resin	4- <i>tert</i> -Butylphenol formaldehyde resin (1.0% pet.)	Colophony (20.0% pet.)
Epoxy resin	PPD (1.0% pet.)	Cyclohexylthiophthalimide (0.5% pet.)
Carba mix	Nickel (II) sulfate hexahydrate (5.0% pet.)	Dibutylphthalate (5.0% pet.)
Black rubber mix	Colophonium (20.0% pet.)	Dibutylthiourea (1.0% pet.)
Cl+ Me – isothiazolinone (MCI/MI)	Formaldehyde (1.0% aq.)	Diphenylthiourea (1.0% pet.)
Quaternium-15	N,N'-Diphenylthiourea (DPTU) (1.0% pet.)	Disperse blue 106 (1.0% pet.)
Methyldibromo glutaronitrile	MBT (2.0% pet.)	Disperse orange 3 (1.0% pet.)
PPD	Diethylthiourea (1.0% pet.)	Dodecylmercaptan (0.1% pet.)
Formaldehyde	1,3-Diphenylguanidine (1.0% pet.)	Formaldehyde (1.0% water)
Mercapto mix	N,N'-Dibutylthiourea (1.0% pet.)	Glutaraldehyde (.2% pet.)
Thiuram mix	Epoxy resin, bisphenol A (1.0% pet.)	Hydroquinone monobenzylether (1.0% pet.)
Panel 3.2	Dodecylmercaptan (0.1% pet.)	Mercapto mix (1.0% pet.)
Diazolidinyl urea	Methylisothiazolinone +	Methylchloroisothiazolinone/methylisothiazolinone (0.01% water)
Quinoline mix	Methylchloroisothiazolinone (0.02% aq.)	Nickel sulfate hexahydrate (2.5% pet.)
Tixocortol-21-pivalate	4-Aminoazobenzene (0.25% pet.)	Octylisothiazolinone (0.025% pet.)
Imidazolidinyl urea	2-n-Octyl-4-isothiazolin-3-one (0.1% pet.)	Potassium dichromate (.25% pet.)
Budesonide	4,4'-Dithiodimorpholine (1.0% pet.)	Thiourea (0.1% pet.)
Hydrocortisone-17-butyrate		Thiuram mix (1.0% pet.)
Mercaptobenzothiazole		
Bacitracin		
Disperse blue 106		

aq., aqueous; IPPD, *N*-isopropyl-*N*-phenyl-4-phenylenediamine; pet., petrolatum; PPD, *p*-Phenylenediamine; MBT, 2-Mercaptobenzothiazole.

suspicious that a patient is hypersensitive to a chemical present in the shoes but otherwise does not react to patch testing. It is possible that the particular sensitizer is in low concentration in the shoe, and ultrasonic bath extraction concentrates it enough to elicit a response in a hypersensitive individual.⁴⁹ Multiple authors recommend the use of chemical analysis of shoe extracts in addition

to patch testing to confirm the presence of the causative chemical in the footwear. Kaniwa et al⁵⁰ were able to identify known and unknown allergens (S-substituted mercaptobenzothiazole compounds and styrenated phenol) through the use of gas chromatography, gas chromatography/mass spectroscopy, direct inlet/mass spectroscopy, and high-performance liquid chromatography.

TABLE 3. Available Products for Shoe ACD⁵⁷⁻⁶⁶

Askin Shoes: www.askin.it ; info@askin.it	Offers products excluding the following materials: Metal tanning agents: chromium salts, aluminum, zirconium, titanium, nickel, lead, copper, cadmium Acids: sulfuric, formic, oxalic, hydrochloric Biocides: trichlorophenol, pentachlorophenol, tributyltin oxide Formaldehyde resins Epoxy resins Amine catalyzers Azoic catalyzers Bactericides Isocyanides Carbamates
Ausangate Socks: www.ausangatesocks.com/default.asp Birkenstock Express: Telephone number: 1-800-451-1459; www.birkenstockexpress.com Birkenstock USA, LP: info@birkenstockusa.com	Lanolin-free socks made of breathable alpaca fiber Offers both cork and polyurethane footbed replacements
The Cordwainer Shop: PO Box 110 67 Candia Rd, Deerfield, NH, 03037; Telephone number: (603) 463-7742; info@cordwainershop.com Loveless Orthopedic Appliance: 4400 SW 21st St, Oklahoma City, OK 73108; Telephone number: 405-631-9731; contact@lovelessboots.com Microair Barrier Socks Alpretec: http://www.alpretec.com/eng for the list of distributors Multnomah Leather Shop: http://www.multnomahleather.com/Allergy Po-Zu: http://www.po-zu.com ; contact@po-zu.com	Sandals and shoes do not use carba mix or specifically the 3 allergens related to carba mix: zinc diethyldithiocarbamate, diphenylguanidine, zinc dibutyldithiocarbamate. In addition, products do not use: abitol, abietic acid, colophony, phthalate, <i>p-tert</i> -butylphenol formaldehyde resin (PTBP-FR), or thiuram mix. Chrome VI is not used in the tanning process of leathers. Soles do not contain mercaptobenzothiazole (MBT). Birkenstock buckles, rivets, and staples are all made of steel and are all nickel free. Glue-free linings for allergy sensitive customers
P.W. Minor and Son, Inc: 3 Tredeasy Ave, Batavia, NY 14020; Telephone number: 800-333-4067; consumerhotline@pwwminor.com Simple Way, The Leather Kit People: www.simpleway.co.uk Snipe: http://www.snipe-shop.de/	Offers hypoallergenic liners for shoes and boots Barrier socks prevent skin from coming in contact with allergens. Offers clogs made of chromate-free vegetable-tanned cowhide. For those with rubber allergy, they use a wood midsole, isolating the wearer's feet from the cemented outsole. Use natural materials, such as hemp, cork, coir, latex (from pure vegetable rubber), wool (100% unbleached and often undyed), and organically tanned leather. Avoid glues.
West Coast Shoe Company: 52828 NW Shoe Factory Lane, PO Box 607 Scappoose, OR, 97056; Telephone number: (800)-326-2711; info@wescoboos.com	Offers hypoallergenic footwear, including chrome-free leather and the use of minimal adhesives Can make shoes to order without adhesives Offers chrome-free tanned leather, natural cotton uppers, nickel-free metal, soles and laces made of natural materials Offers chrome-free vegetable-tanned leather products

Nishioka et al⁵¹ made the first report of 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (ETMDQ) as an allergen in rubber boots by identifying it through gas chromatography/mass spectroscopy.

The variation in allergen sensitivity across studies is attributed to the variation in chemical composition of footwear, individual susceptibility, and patch testing series used.³ Furthermore, differences in footwear styles across regions, as well as differences in climate, can impact the variation in the predominant allergens documented in different studies. It has been reported that allergy to chromium compounds is frequent in European countries and in India, whereas allergy to rubbers and adhesives is more common in North America and Asia.⁸

Management

Once the causative agent is determined, patients should avoid exposure to the allergen completely by changing shoe materials or avoiding contact with them through the use of barriers. Avoiding the allergen can present a challenge, and various strategies may need to be used. For those allergic to chromium, chromium-free leather shoes are a viable substitute; otherwise, it is advised to switch to a new pair of leather shoes every few months because chromium may filter out from the leather over time as they get worn out.⁸ Wearing 2 pairs of socks and alternating different pairs of boots on a day-to-day basis have also proven to be helpful for some patients with an occupational allergy to work boots. Patients with rubber allergy should consider replacing the innersoles with cork, composite, or felt and using a nonrubber cement adhesive. Custom-made shoes, although more expensive, are another option.¹ Table 3 provides a list of custom shoe manufacturers and available footwear products for patients with ACD.

Barrier socks, developed through textile engineering, are a more recent form of treatment used to protect the skin against shoe allergens. Socks manufactured by Alpretec are made of a 3-layer fabric designed to be impermeable to allergens, irritants, and liquids. Corazza and colleagues⁵² tested the efficacy of these socks in 9 patients with ACD. After 8 weeks, 7 of 9 patients reported reduction in pain, and 6 of 9 reported a reduction in itch; all patients reported improvement in their ability to walk. Such socks may be a feasible alternative when complete avoidance of a causative agent is difficult. Hyperhidrosis should also be treated because sweat can cause chemicals to seep out from shoes, further contributing to contact allergy.¹

Occasional use of topical and systemic corticosteroid therapies may be beneficial in managing ACD.⁹ Barrier creams have been shown to improve ACD in experimental settings, but their efficacy in clinical use remains uncertain.^{53,54} Some reports indicate that the use of barrier creams further exacerbate cases of ACD.⁵³ Clotrimazole and other chelating agents have shown to prevent nickel ACD by binding the nickel present on the skin.⁵⁵

In 1 study that followed 48 patients for several years after being diagnosed with shoe ACD, approximately 87.5% of patients had

their shoe dermatitis improve or resolve after a mean follow-up period of 2.9 years.¹ Forty-three percent of patients were atopic, a poor prognostic factor in which patients usually do not experience clearance of the dermatitis after avoidance of the culprit allergen.^{1,6} Many of these patients, however, found relief of their symptoms by finding alternative shoes and by using different strategies of allergy avoidance.

Allergic contact dermatitis can be a significant problem not only in adults but also in children. Teixeira et al⁵⁶ described the case of a 5-year-old child with severe foot dermatitis that prevented her from attending school, greatly impacting her psychosocial development. In persistent cases of foot dermatitis in children, patch testing is advised.

CONCLUSIONS

Foot dermatitis is a common and treatable condition. Allergic contact dermatitis of the feet should be considered in the differential in cases of persistent foot dermatitis. Patch testing is crucial for determining the offending allergens, and once determined, specific strategies can be used to eliminate or minimize contact. Although managing this condition may present challenges, the prognosis for ACD is good overall. Additional multicenter studies on the international and national levels are needed to determine the most applicable footwear screening series by region. Strict regulation and discovery of toxic allergens such as DMF will be vital in continuing to prevent and manage this condition in the future.

REFERENCES

- Freeman S. Shoe dermatitis. *Contact Dermatitis* 1997;36(5):247–251.
- Chowdhuri S, Ghosh S. Epidemio-allergological study in 155 cases of footwear dermatitis. *Indian J Dermatol Venereol Leprol* 2007;73:319–322.
- Saha M, Srinivas CR, Shenoy SD, et al. Footwear dermatitis. *Contact Dermatitis* 1993;28(5):260–264.
- Rani Z, Hussain I, Haroon TS. Common allergens in shoe dermatitis: our experience in Lahore, Pakistan. *Int J Dermatol* 2003;42(8):605–607.
- Shackelford KE, Belsito DV. The etiology of allergic-appearing foot dermatitis: a 5-year retrospective study. *J Am Acad Dermatol* 2002;47(5):715–721.
- Lazzarini R, Duarte I, Marzagão C. Contact dermatitis of the feet: a study of 53 cases. *Dermatitis* 2004;15(3):125–130.
- Warshaw EM, Schram SE, Belsito DV, et al. Shoe allergens: retrospective analysis of cross-sectional data from the North American Contact Dermatitis Group, 2001–2004. *Dermatitis* 2007;18(4):191–202.
- Landeck L, Uter W, John SM. Patch test characteristics of patients referred for suspected contact allergy of the feet—retrospective 10-year cross-sectional study of the IVDK data. *Contact Dermatitis* 2012;66:271–278.
- Onder M, Atahan AC, Bassoy B. Foot dermatitis from the shoes. *Int J Dermatol* 2004;43(8):565–567.
- Oumeish OY, Rushaidat QM. Contact dermatitis to military boots in Jordan. *Contact Dermatitis* 1980;6(7):498.

11. Friis UF, Johansen JD, Krongaard T, et al. Quantitative assessment of diethylthiourea exposure in two cases of occupational allergic contact dermatitis. *Contact Dermatitis* 2011;64(2):116–118.
12. Roberts JL, Hanifin JM. Athletic shoe dermatitis contact allergy to ethyl butyl thiourea. *JAMA* 1979;241(3):275–276.
13. Liippo J, Ackermann L, Hasan T, et al. Sensitization to thiourea derivatives among Finnish patients with suspected contact dermatitis. *Contact Dermatitis* 2010;63(1):37–41.
14. Belsito DV. Common shoe allergens undetected by commercial patch-testing kits: dithiodimorpholine and isocyanates. *Am J Contact Dermat* 2003;14(2):95–96.
15. Nedorost S. Clinical patterns of hand and foot dermatitis: emphasis on rubber and chromate allergens. *Dermatol Clin* 2009;27(3):281–287.
16. Fortina AB, Piaserico S, Larese F, et al. Diaminodiphenylmethane (DDM): frequency of sensitization, clinical relevance and concomitant positive reactions. *Contact Dermatitis* 2001;44(5):283–288.
17. Grimalt R, Vilaplana J, Romaguera C. Three cases of allergic contact dermatitis to 4,4'-diaminodiphenylmethane. *Contact Dermatitis* 2009;60(6):346–347.
18. Bendewald MJ, Farmer SA, Davis M. An 8-year retrospective review of patch testing with rubber allergens: the Mayo Clinic experience. *Dermatitis* 2010;21(1):33–40.
19. Castaneda-Tardan MP, Gelpi C, Jacob SE. Allergic contact dermatitis to Crocs. *Contact Dermatitis* 2008;58:248–249.
20. Zimerson E, Bruze M. Contact allergy to the monomers in *p*-tert-butylphenol-formaldehyde resin. *Contact Dermatitis* 2002;47(3):147–153.
21. Holden CR, Gawkrödger DJ. 10 years' experience of patch testing with a shoe series in 230 patients: which allergens are important? *Contact Dermatitis* 2005;53(1):37–39.
22. Hausen BM, Krohn K, Budianto E. Contact allergy due to colophony (VII): sensitizing studies with oxidation products of abietic and related acids. *Contact Dermatitis* 1990;23(5):352–358.
23. Bangsgaard N, Thyssen JP, Menné T, et al. Contact allergy to epoxy resin: risk occupations and consequences. *Contact Dermatitis* 2012;67(2):73–77.
24. Srinivas CR, Devadiga R, Aroor AR. Footwear dermatitis due to bisphenol A. *Contact Dermatitis* 1989;20(2):150–151.
25. Nardelli A, Taveirne M, Drieghe J, et al. The relation between the localization of foot dermatitis and the causative allergens in shoes: a 13-year retrospective study. *Contact Dermatitis* 2005;53:201–206.
26. Vidović R, Kansky A. Contact dermatitis in workers processing polyvinyl chloride plastics. *Derm Beruf Umwelt* 1985;33(3):104–105.
27. Hansen MB, Johansen JD, Menne T. Chromium allergy: significance of both Cr(III) and Cr(VI). *Contact Dermatitis* 2003;49:206–212.
28. Thyssen JP, Strandesen M, Poulsen PB, et al. Chromium in leather footwear—risk assessment of chromium allergy and dermatitis. *Contact Dermatitis* 2012;66(5):279–285.
29. Hansen MB, Menné T, Johansen JD. Cr(III) reactivity and foot dermatitis in Cr(VI) positive patients. *Contact Dermatitis* 2006;54:140–144.
30. Thyssen JP, Jellesen MS, Møller P, et al. Allergic chromium dermatitis from wearing 'chromium free' footwear. *Contact Dermatitis* 2014;70:183–192.
31. Minkin W, Cohen HJ, Frank SB. Contact dermatitis to East Indian leather. *Arch Dermatol* 1971;103(5):522–523.
32. Rantanen T. The cause of the Chinese sofa/chair dermatitis epidemic is likely to be contact allergy to dimethylfumarate, a novel potent contact sensitizer. *Br J Dermatol* 2008;159(1):218–221.
33. Mercader P, Serra-Baldrich E, Alomar A. Contact dermatitis to dimethylfumarate in armchairs. *Allergy* 2009;64(5):818–819.
34. D'Erme AM, Bassi A, Lotti T, et al. Dimethyl fumarate contact dermatitis of the foot: an increasingly widespread disease. *Int J Dermatol* 2012;51(1):42–45.
35. Toledo F, Silvestre JF, Cuesta L, et al. Correlation between lesion site and concentration of dimethyl fumarate in different parts of shoes in patients with contact dermatitis caused by dimethyl fumarate in footwear. *Contact Dermatitis* 2011;65(2):92–95.
36. Giménez-Arnau A, Silvestre JF, Mercader P, et al. Shoe contact dermatitis from dimethyl fumarate: clinical manifestations, patch test results, chemical analysis, and source of exposure. *Contact Dermatitis* 2009;61(5):249–260.
37. Silvestre JF, Toledo F, Mercader P, et al. Spanish Research Group of Allergic Contact Dermatitis due to Dimethyl Fumarate in Spain. A summary of shoe allergic contact dermatitis caused by dimethyl fumarate in Spain. *Contact Dermatitis* 2011;65(2):122–123.
38. Goossens A, Bedert R, Zimerson E. Allergic contact dermatitis caused by nickel and cobalt in green plastic shoes. *Contact Dermatitis* 2001;45(3):172.
39. Koch P, Nickolaus G. Allergic contact dermatitis and mercury exanthem due to mercury chloride in plastic boots. *Contact Dermatitis* 1996;34(6):405–409.
40. Opie J, Lee A, Frowen K, et al. Foot dermatitis caused by the textile dye basic red 46 in acrylic blend socks. *Contact Dermatitis* 2003;49(6):297–303.
41. Slodownik D, Williams J, Tate B, et al. Textile allergy—the Melbourne experience. *Contact Dermatitis* 2011;65(1):38–42.
42. Jordan WP, Bourlas MS. Allergic contact dermatitis to underwear elastic. *Arch Dermatol* 1975;111:593–595.
43. Blancas-Espinosa R, Ancona-Alayón A, Arévalo-López A. Allergic contact dermatitis to socks presenting as bleached rubber syndrome. *Am J Contact Dermat* 2000;11(2):97–98.
44. Rietschel RL. Role of socks in shoe dermatitis. *Arch Dermatol* 1984;120(3):398.
45. Hatch KL, Maibach HI. Textile fiber dermatitis. *Contact Dermatitis* 1985;12(1):1–11.
46. Perez-Crespo M. Contact dermatitis due to stockings. *Dermatitis* 2009;20(4):221.
47. Imbeau SA, Reed CE. Nylon stocking dermatitis. *Contact Dermatitis* 1979;5:163–164.
48. Epstein E. Shoe contact dermatitis. *JAMA* 1969;209(10):1487–1492.
49. Bruze M, Trulsson L, Bendsøe N. Patch testing with ultrasonic bath extracts. *Am J Contact Dermat* 1992;3(3):133–137.
50. Kaniwa M, Momma J, Ikarashi Y, et al. A method for identifying causative chemicals of allergic contact dermatitis using a combination of chemical analysis and patch testing in patients and animal groups: application to a case of rubber boot dermatitis. *Contact Dermatitis* 1992;27:166–173.
51. Nishioka K, Murala M, Ishikawa T, et al. Contact dermatitis due to rubber boots worn by Japanese farmers, with special attention to 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (ETMDQ) sensitivity. *Contact Dermatitis* 2006;35(4):241–245.
52. Corazza M, Baldo F, Ricci M, et al. Efficacy of new barrier socks in the treatment of foot allergic contact dermatitis. *Acta Derm Venereol* 2011;91(1):68–69.
53. Alvarez MS, Brown LH, Brancaccio RR. Are barrier creams actually effective? *Curr Allergy Asthma Rep* 2001;1(4):337–341.
54. Goh CL, Gan SL. Efficacies of a barrier cream and an afterwork emollient cream against cutting fluid dermatitis in metalworkers: a prospective study. *Contact Dermatitis* 1994;31(3):176–180.
55. Gawkrödger DJ, Healy J, Howe AM. The prevention of nickel contact dermatitis. A review of the use of binding agents and barrier creams. *Contact Dermatitis* 1995;32(5):257–265.
56. Teixeira M, Machado S, Teixeira A, et al. Severe contact allergy to footwear in a young child. *Contact Dermatitis* 2005;52(3):159–160.
57. Rietschel RL, Fowler JF. *Fisher's Contact Dermatitis*, 5th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:309.

58. American Contact Dermatitis Society. Available at: <http://www.contactderm.org/i4a/pages/index.cfm?pageid=3291>. Accessed February 15, 2014.
59. Askinshoes. Available at: <http://www.askin.it/eng/home.php>. Accessed February 15, 2014.
60. Ausangate Socks. Available at: <http://www.ausangatesocks.com/default.asp>. Accessed February 15, 2014.
61. Birkenstock Express. Available at: <http://www.birkenstockexpress.com/>. Accessed February 15, 2014.
62. Birkenstock. Available at: <https://www.birkenstockusa.com/>. Accessed February 15, 2014.
63. Alpretec: Allergy Prevention Technology. Available at: <http://www.alpretec.com/eng/pathologies/contact-dermatitis/microair-barrier-and-the-contact-dermatitis.html>. Accessed February 15, 2014.
64. Po-Zu. Available at: <http://po-zu.com/roto/>. February 15, 2014.
65. Simple Way. Available at: <http://www.simpleway.co.uk/>. February 15, 2014.
66. Snipe. Available at: <http://www.snipe-shop.de/>. February 15, 2014.