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Systemic Contact Dermatitis

Marcella Aquino[1,2] · Greg Rosner[2]

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Abstract

Systemic contact dermatitis (SCD) traditionally refers to a skin condition where an individual who is cutaneously sensitized to an allergen will subsequently react to that same allergen or a cross reacting allergen via a different route. It occurs to allergens including metals, medications, and foods. The exact pathophysiology underlying this disease remains unknown, although it appears to be mediated by type 4 hypersensitivity reactions and possibly type 3 hypersensitivity reactions. The p-I concept (pharmacologic interaction with immunoreceptors) hypothesized that drugs are able to bind directly to a T cell receptor without first being presented by MHC (major histocompatibility complex) molecules and without prior metabolism, which would help explain why SCD can be seen on first exposure to medications. Nomenclature remains a challenge as SCD can be subcategorized using terms such as ACDS (allergic contact dermatitis syndrome) and its four clinical stages, Baboon syndrome, and SDRIFE (symmetrical drug-related intertriginous and flexural exanthema), which share many overlapping features. Food allergens may be responsible for uncontrolled or persistent symptoms in patients with contact dermatitis who do not respond to topical avoidance. With medications, symptoms may be induced by topical application versus systemic administration. Patch testing (PT) may be beneficial in diagnosing SCD caused by metals and many topical medications including corticosteroids, antimicrobials (ampicillin, bacitracin, erythromycin, neomycin, nystatin), NSAIDs (diclofenac, ibuprofen), anesthetics, and antihistamines (chlorphenamine, piperazine). Current treatment options include topical steroids and oral antihistamines for symptom relief and dietary avoidance to causative foods or metals.

Keywords Systemic contact dermatitis · Baboon syndrome · Patch test · Avoidance diets

Abbreviations

ACD	Allergic contact dermatitis
ACDS	Allergic contact dermatitis syndrome
BOP	Balsam of Peru
BS	Baboon syndrome
CS	Corticosteroids
LND	Low nickel diet
PT	Patch test
MHC	Major histocompatibility complex
SCD	Systemic contact dermatitis
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema

✉ Marcella Aquino
marcella.aquino@nyulangone.org

Greg Rosner
gregory.rosner@nyulangone.org

[1] SUNY at Stony Brook, Stony Brook, NY, USA

[2] Division of Rheumatology, Allergy & Immunology, NYU Winthrop University Hospital, 120 Mineola Blvd, Suite 410, Mineola, NY 11501, USA

Introduction

Systemic contact dermatitis (SCD) refers to a skin condition where an individual who is sensitized to an allergen via the cutaneous route will subsequently react to that same allergen or a cross reacting allergen via the systemic route (oral, intravenous, intramuscular, inhalational, transmucosal, or transcutaneous) [1, 2]. It can manifest as a rash at the previous site of dermatitis, rash at the site of a previous positive patch test, vesicular hand dermatitis (most commonly from nickel, cobalt, or chrome allergy but also from foods), pruritic papules on elbows and knees, erythroderma, and vasculitis-like lesions [1, 3].

More recently, it has been recognized as a cause of persistent contact dermatitis in patients who are refractory to traditional treatments especially for patients with contact dermatitis to foods as patients may not be aware that they are ingesting

their contact allergen [4]. Patients may present with systemic symptoms as well as rash including nausea, vomiting, diarrhea, fever, malaise, headaches, and arthralgia [5]. SCD occurs to allergens including metals (mercury, nickel), medications, and foods (Balsam of Peru) including plants and herbal products usually within 1 to 2 days of exposure. In the 1980s, SCD to metals and antibiotics was described as "Baboon syndrome" (BS) by Andersen et al. due to the erythematous lesions on the buttocks, inner thighs, and axilla that resembled the red bottomed baboon [6].

Pathophysiology

The precise mechanism underlying SCD reactions remains yet to be clearly defined. Most of our current knowledge about the pathophysiology of SCD is mainly based on patients sensitized to the metals (mercury, nickel, and gold); thus, these results cannot be definitively extrapolated to drug-elicited reactions, although the mechanisms are thought to be similar.

There are several studies supporting a type 4 hypersensitivity reaction involved in the pathogenesis of SCD [7–10]. Originally, the pathologic mechanism of SCD was thought to be similar to that of allergic contact dermatitis (ACD) [11]. After metabolism of the causative drug in the skin, a hapten-carrier complex is processed by antigen-presenting cells and leads to clonal expansion of T cells in the local lymph node, which can then migrate to the skin and develop a cytotoxic response [11]. In 2004, Jensen et al. [12] demonstrated that patients with a history of SCD to nickel had a significantly higher fraction of CD3+, CD4+, and CD8+ memory (CD45RO+) T cells that contain the skin homing receptor called cutaneous lymphocyte-associated antigen (CLA) than non-nickel-sensitized healthy controls. In that same study, those patients were provoked with oral nickel and were subsequently found to have a decrease in blood memory T cells (mainly the CD8+ CD45RO+ CLA+ T cells), which suggested that the cells had migrated to the skin.

In 2007, Posadas et al. [13] introduced a novel mechanism called the p-I concept (pharmacologic interaction with immunoreceptors). The p-I concept hypothesized that drugs are able to bind *directly* to a T cell receptor without first being presented by MHC (major histocompatibility complex) molecules and without prior metabolism. The p-I concept can help explain several aspects of drug reactions including reactions that occur on first exposure to the drug, why the reaction is observed within only a few hours or days, and why higher doses of medications are often associated specifically with SCD [13].

In 2009, Lachapelle [14] proposed the term ACDS (allergic contact dermatitis syndrome) to be used for patients with prior cutaneous sensitization instead of SCD or BS. The four clinical stages of ACDS were proposed as follows: stage 1—localized ACDS; stage 2—regional dissemination of ACDS via lymphatic vessels; stage 3A—hematogenous dissemination of ACDS to distant sites (generalized dissemination of skin lesions from the primary site of application via blood vessels); stage 3B—systemic reactivation of ACDS via ingestion, inhalation, or injection of the allergen. Thus, drug-related Baboon syndrome (BS) with a previous cutaneous sensitization would be due to either stage 3A or 3B of ACDS. However, cases of drug-related Baboon syndrome *without* a previous cutaneous sensitization cannot be categorized as stage 3A or 3B of ACDS.

In 2004, Hausermann [15] came up with the term SDRIFE (symmetrical drug-related intertriginous and flexural exanthema), to describe systemically induced drug-related Baboon syndrome *without* previous exposure. Hausermann proposed five diagnostic criteria for SDRIFE: (1) exposure to a systemically administrated drug; (2) sharply demarcated erythema of the gluteal area and/or V-shaped erythema of the inguinal/perigenital area; (3) involvement of at least one other intertriginous/flexural localization; (4) symmetry of affected areas; and (5) absence of systemic symptoms and signs.

Ozkaya [16] suggested sub-classification based on the causative agent and previous sensitization. They used the group names: contact allergen-induced BS (excluding drugs), contact allergenic drug-induced BS, and non-contact allergenic drug-induced BS. The last group is synonymous with SDRIFE. Miyahara et al. [17] used the term classical BS to describe contact allergen-induced BS (excluding drugs); topical drug-induced BS to describe ACDS stage 3A; systemic drug-induced BS to describe ACDS stage 3B; and non-contact allergenic drug-induced BS as SDRIFE (Table 1).

There is less evidence that a type 3 hypersensitivity reaction (antigen-antibody complexes) is involved in the pathophysiology in SCD although the rapid appearance of cutaneous symptoms after systemic administration, combined with the identification of antibodies against the hapten-albumin complex in the blood, supports this mechanism [18, 19].

SCD to Medications

Acral and anogenital erythemas are a commonly reported with SCD to medications. SDRIFE has been reported in children and adults and may have a male preponderance [20]. There is usually a latency period of a few hours to a few days for SDRIFE [20].

Topical Drug-Induced SCD

Drugs that have caused SCD from topical absorption include ampicillin, corticosteroids, NSAIDs (bufexamac, diclofenac), acetylsalicylic acid, anesthetics (cinchocaine), antibiotics (neomycin), and ethylenediamines [1, 2].

Table 1 SCD to drugs: various classifications according to authors

	Lachapelle [14]	Miyahara [17]	Ozkaya [16]
Drug-induced via topical administration	ACDS stage 3A	Topical drug-induced	Contact allergic drug-induced BS
Drug-induced via systemic administration	ACDS stage 3B	Systemic drug-induced	Non-contact allergenic drug-induced

Aminosalicyclic Acid

A 50-year-old male [21] developed erythematous rash on buttocks, anogenital area, and arms after the application of 5-amcinosalicyclic acid foam to treat hemorrhoids. He was patch test positive to the foam at 10% concentration in petrolatum and his rash resolved with discontinuation of this drug.

NSAIDs

A 39-year-old female [22] who was breastfeeding developed rash on her breast, left arm, chest, neck, and cheek after contact with bufexamac topically that she was applying to her infant child due to eczema. The patient was patch test (PT) positive to bufexamac. A 48-year-old woman [23] presented with an acute erythematous, maculopapular exanthem in the anogenital area several days after applying a bufexamac-containing ointment to the anal region. She was PT positive to bufexamac. Due to its high risk of causing contact allergy, in April 2010, the European Medicines Agency's Committee for Medicinal Products for Human Use [24] recommended that marketing authorizations for bufexamac-containing medicines be revoked.

In the case of diclofenac, a 37-year-old female [25] developed rash at application site on her knees along with a generalized rash, fever, malaise, and facial swelling. She had been prescribed both topical and oral diclofenac for knee pain and within 24 h developed these symptoms. Skin biopsies were obtained from the rash on her knees (spongiosis with intraepidermal vesicles perivascular lymphocytic and eosinophilic infiltrate) and generalized rash (spongiosis, lymphocytic exocytosis, and interface dermatitis with superficial dermal edema and perivascular lymphocytic infiltration) but PT was declined by the patient.

Edetate Disodium

Edetate disodium is the salt of ethylenediaminetetracectic acid (EDTA) and is widely used in preservatives, antioxidants, and medications of the eyes and nose. A recent case report presents a 76-year-old man [26] with history of episodic erythematous eruption occurring primarily over the buttocks for 9 months and lasting 1 week before desquamating almost always associated with use of azelastine nasal spray. Patch testing was negative to azelastine nasal spray, pure azelastine (0.1 to 10%) in both petrolatum and aqueous solutions. The patient developed symptoms within 12 h of placement of the patch with edetate disodium 1% when allergens were patch tested individually.

Topical Clioquinol/Hydrocortisone Combination Cream

Clioquinol is a hydroxyquinoline used to treat fungal or parasitic infections. A 3-year-old female was prescribed topical clioquinol/hydrocortisone combination cream [27] for use to the vaginal area due to a complaint of urogential burning. After 2 days of use, she developed a painful, erythematous, eruption around her neck which spread to involve her bilateral axillae, antecubital fossae, groin, and perioral area. PT was not performed as her parents declined.

Topical Anesthetics

Cinchocaine is a topical anesthetic of the amide class, frequently used in health care preparations. A 43-year-old woman [28] developed an intertriginous exanthema 3 days after anal application of Nupercainal®, a cinchocaine cream for hemorrhoids. The patient was advised to stop the drug and was treated with systemic corticosteroids. Patch tests were positive (3+) to cinchocaine 5% and other topical anesthetics. A 62-year-old woman [29] presented with erythematous rash of the face, axillae, elbow flexures, and inner thighs, after several days of application of DoloPosterine® (active ingredient is cinchocaine) ointment to the perianal skin and rectal mucosa for hemorrhoids. Lesions cleared with oral prednisolone and drug discontinuation. She was PT positive to the commercial drug and cinhocaine.

Systemic Drug-Induced SCD

Medications taken orally or IV which have induced SCD include ethylenediamine, neomycin, nystatin, erythromycin, and corticosteroids.

Gold

Aside from its use in jewelry, gold can be ingested via medications and has been used in dentistry materials. A 76-year-old female with history of earlobe swelling with gold earrings developed a pruritic generalized vesicular eruption associated with malaise and low-grade temperature. The patient was PT positive to gold sodium thiosulfate on day 3 (3+ positive). The patient had been ingesting a homeopathic medication named Aurocard® which contained gold. Upon stopping the medication, her eczema cleared within 4 weeks and the patient remained asymptomatic 5 months later [30]. In a 52-year-old female [31] with a history of delayed positive PT to gold, an intramuscular introduction of gold as therapy for rheumatoid arthritis led to reactivation of her previously positive PT.

Corticosteroids (CS)

Although rare [32], reactions to systemic corticosteroids (CS) do occur even in patients without a history of previous cutaneous exposure. A current chemical classification for CS is split into three groups based on a plane structural analysis of the CS [33]. Group I includes CS without methyl group on carbon (C) 16 and *without a diol* on C16-C17; group II includes CS without methyl group on carbon 16 but *with a diol* on C16-C17; and group III includes CS with methyl group on carbon 16. As there are only few cross-reactions between these groups, finding an alternative topical CS is often not difficult because a patient allergic to a group I CS can theoretically tolerate a topical CS belonging to groups II or III. Barbard and Waton [34] looked at 79 cases of reactions to systemic CS previously published and applied the above classification by Baeck. They found that 57 patients (72%) had a negative PT to a CS within the same group that they were sensitized too. They thus proposed in patients with a history of reactions to a systemic CS and negative skin tests, to obtain PT to CS, even if these CS belong to the same group of those responsible for the initial adverse reaction. Of note, PT to CS should be read at 48 h, 72–96 h, and 7–10 days, since a late positive result may occur.

Reactions to CS have included deflazacort which is a corticosteroid drug approved to treat Duchenne muscular dystrophy; in the literature, both delayed and acute type reactions in a small group of patients have been noted [35, 36]. A 50-year-old female [37] with history of allergic rhinitis and rash to previous administrations of CS was positive to betamethasone, dexamethasone, prednisolone, and methylprednisolone via skin prick, intradermal testing (either immediate or delayed reading), and/or PT. She developed a symmetric, erythematous maculopapular rash in her gluteal, perianal, intertriginous, and flexural areas 12 h after oral challenge to betamethasone. She had positive challenges as well to dexamethasone, hydrocortisone, and cloprednol.

Antibiotics

Neomycin is the 4th most common positive allergen on PT in North America [38]; it is highly cross-reactive with gentamycin, tobramycin, and streptomycin. Patients who become sensitized through the skin, likely due to its frequent inclusion in over-the-counter topical antibiotic preparations, may react to orally administered aminoglycosides [39]. A 74-year-old female [40] developed widespread rash within a few days after knee replacement with gentamicin impregnated bone cement which lasted a few weeks. She was PT positive to gentamicin but not metals suggesting that the antibiotic was the culprit; a possible explanation for the resolution of the rash spontaneously was that the drug releases maximum amounts initially and then decreases over time.

A 28-year-old man [41] developed an erythematous pruritic eruption affecting his inner thighs, buttocks, and axillae 8 days after starting amoxicillin for an upper respiratory infection. The eruption resolved completely after 1 week without any therapy. Patch testing to amoxicillin (5, 10 and 30% in petrolatum and in water) was negative. Similarly, a 35-year-old male [41] also developed an erythematous eruption on his inner thighs and buttocks 4 days after he was started on amoxicillin and clavulanic acid (Augmentin®) for a periodontal abscess. The rash resolved once the patient was switched to an alternative antibiotic.

Other implicated antibiotics include the cephalosporins (cephalexin and cefuroxime) [15, 41] erythromycin [42], and clindamycin [43].

Antihistamines

Patients sensitized to ethylenediamine who ingest oral antihistamines of the same class may develop symptoms. Hydroxyzine is a piperazine derivative that is structurally similar to ethylenediamine. A 48-year-old female [44] developed a red, scaly rash on her trunk and extremities after ingesting oral hydroxyzine. Patch testing revealed 3+ positive to ethylenediamine; with reintroduction of the drug on consecutive nights, the rash recurred. Another female patient [45] developed widespread rash after the use of a topical agent containing ethylenediamine and oral ingestion of cetirizine and levocetrizine (second-generation piperazines); she was PT positive to ethylenediamine and the rash resolved after discontinuation of the antihistamines.

Aminophylline (a combination of theophylline and ethylenediamine) produced an erythematous rash in the buttocks, groin, neck, and axilla in a 66-year-old female [46]

given the medication intravenously for a COPD exacerbation and in a 68-year-old female [47] prescribed oral aminophylline for COPD who developed a rash on her left scapular region, trunk and thighs-patch testing was positive to ethylenediamine in both patients.

NSAIDs

A 60-year-old male [41] patient presented with an erythematous, purpuric, eruption located on the inguinal and axillary regions and the buttocks. He had ingested naproxen tablets for low back pain the day prior. Upon stopping the drug, there was a rapid improvement within a few days and complete resolution within 1 week without any other therapy. PT to naproxen (1, 2, 5, 10, and 20% concentrations) was negative at 48, 72, and 96 h.

SCD to metals

Nickel is the most common PT allergen [38], and exposure includes coins, jewelry, tools, clothing, utensils, nickel-plated objects (phones, lab tops), and food. Canned foods, cocoa, chocolate, soy, legumes, herring, salmon, shellfish, cashews, and mackerel are examples of foods with high nickel content [48]. Sensitization to nickel likely also occurs via ear [49] and body piercings. In Europe after the institution of EU Nickel Directive, the prevalence of nickel allergy decreased in Danish young women [50].

Mercury

Classically, SCD (contact non-drug induced) was reported in patients sensitized to mercury. These patients had previous sensitization topically via the use of mercurochrome from its placement in antiseptics and thimerosal in ophthalmic preparations and vaccines. Symptoms would then occur via inhalation of evaporated mercury from a broken thermometer or ingestion of mercury from dental fillings or medications [17]. Overall, use of mercury has declined due to its toxicity but it is still found in the production of chlorine and caustic soda, thermometers, certain cosmetics (mascara), and foods (seafood) [51]. SCD from mercury tends to occur in both sexes at any age and is predominantly reported from European countries and Japan [17, 52, 53].

Zinc

Although uncommon, there are reported cases of SCD to zinc. Zinc is utilized in dental work, in industry (paints, alloys), batteries, and as anti-corrosive agent [51]. A 61-year-old male [54] presenting with generalized vesicular rash was PT positive to zinc chloride (2+). The patient's dermatitis improved with replacement to zinc free fillings. In another case report [55], a 37-year-old Japanese male with 1-year history of pruritic widespread skin eruptions had dental fillings 3 months prior to onset of rash. He was PT positive to zinc (1+) and had a positive lymphocyte stimulation test to zinc. Overall removal of the zinc containing fillings leads to improvement of the rash with brief flare ups associated with each procedure.

Nickel

A 15-year-old female who developed an erythematous dermatitis on face, neck, scalp, arms, and wrists 40 days after placement of orthodontic appliances [56] was found to be PT positive to nickel (2+). Removal of the appliances led to resolution of symptoms within 6 months and sustained symptom free interval after 2 years.

Food Induced

Balsam of Peru (BOP), known for its presence in fragrance [57], as well as a sweetening agent in a number of cinnamates, and vanillins, has been recognized as a common dietary cause of SCD [58]. It is a resin also used in the medicinal and pharmacologic industries due to antiseptic properties [51]. BOP is found commonly in many foods/drinks including the following: citrus fruits; spices such as cinnamon; condiments such as ketchup; pickles; drinks such as wine, beer, and gin; chocolate; ice cream; tomatoes; and Cola or other spiced soft drinks. Even patients with a positive PT to fragrance mix but negative to BOP can still experience SCD from these types of foods/flavoring agents [4].

Aspartame a commonly used artificial sweetener that is converted in the liver to formaldehyde has been implicated in SCD [59]. It can be found in chewable vitamins, diet drinks, and low-calorie foods [60]. Matiz and Jacob [61] reported a case of an 11-year-old boy with SCD (generalized erythema and eyelid dermatitis) who improved with discontinuation of his Montelukast (Singulair™, Merck&Co., Inc., Whitehouse Station, NJ) chewable tablets (contained aspartame). Interestingly, the vast majority of formaldehyde-allergic patients are not symptomatic, as it requires an enormous amount of daily aspartame consumption before formaldehyde begins to accumulate. Thus, only patients with positive PT to formaldehyde that do not clear with topical avoidance should be counseled to avoid aspartame [51].

Sorbic acid, commonly used in toothpaste, has classically been implicated in perioral contact dermatitis and recently in SCD manifesting as vesicular eczema [62]. It is also found in foods such as strawberries, prunes, and cheese [63] and is chemically identical to potassium sorbate used to keep items fresh [4]. Thus, potassium sorbate should also be avoided in

patients allergic to sorbic acid. A sorbic acid avoidance diet has been proposed [64].

Garlic has been demonstrated to cause a chronic vesicular hand eczema [65]. It is believed to cross react with BOP; therefore, garlic diet removal has been suggested in the BOP free diet [66].

Propolis A resin produced by honeybees, it can be found in cosmetic products, syrups, lozenges, and tablets, and has been implicated in several cases of ACD; its main sensitizers are 3-methyl-2-butenyl caffeate, and phenylethyl caffeate [51]. In 2011, a case was reported of a 36-year-old female patient who ingested propolis syrup as a holistic health therapy, and subsequently developed papules and patches on the face, neck, arms, and abdomen [67].

Propylene Glycol Recently named the American Contact Dermatitis Society's Allergen of the Year for 2018 [68], propylene glycol is commonly used as a thickening agent in foods such as dressings, snacks, baked goods, and beverages [69]. Propylene glycol is also used in medicaments and personal products such as cosmetics and fragrances due to its properties as a solvent, vehicle, and emulsifier [70]. It has been reported to cause pruritic eczematous plaques on the face, neck, and hand [70].

Chamomile: Many individuals drink Chamomile tea regularly as it is believed to have beneficial effects including anti-inflammatory and antispasmodic effect. It is also applied topically for healing ulcers, wounds, and eczema. Chamomile tea has previously been reported as causing SCD via topical use [71] as well as oral use [72]. In 2003, a case of a 22-year-old female with relapsing episodes of facial eczema, secondary to chamomile tea, was reported [73] (Table 2).

Diagnosis

SCD has a broad spectrum of differential diagnoses ranging from infections to bullous diseases. Allergic and irritant contact dermatitis should be ruled out on the basis of the clinical presentation and the patient's history.

Patch Testing to Drugs

Certain medications are currently commercially available for PT facilitating easy administration and include corticosteroids, antimicrobials (ampicillin, bacitracin, erythromycin, neomycin, nystatin), NSAIDs (diclofenac, ibuprofen), anesthetics, and antihistamines (chlorphenamine, piperazine). Other drugs can be tested as follows: pure drugs at a 10% dilution in petrolatum and 10% dilution in alcohol [74]. Medications in their commercialized form should have their coating removed and be ground to a fine powder which can be tested as is, as well as incorporated at 30% in white petrolatum and diluted to 30% in water [74]. Guidelines for PT to medication-induced reactions come from both the European Society of Contact Dermatitis (ESCD) [74] and the European Network on Drug Allergy (ENDA) [75]. The ESCD recommends waiting 6 weeks to 6 months after healing of the adverse drug reaction before PT, while the ENDA advises a wait time of 3 weeks to 3 months. The ESCD recommends reading the drug PT at 20 min, day 4 and if negative on day 4, a day 7 reading is also suggested. In contrast, the ENDA recommends readings on day 2 and on day 3 or 4 only. Overall PT for drugs has yielded conflicting results, as some patients with negative PT have had a positive oral challenge [15].

Treatment

Overall, SCD is a benign process. Skin eruptions tend to resolve with desquamation after a few weeks once the culprit has been stopped. Post-inflammatory hyperpigmentation has not been reported [17]. Treatment is aimed at symptomatic relief with oral antihistamines and topical corticosteroids. More severe cases may require a brief course of systemic corticosteroid therapy.

For Nickel Allergy

Therapy for nickel allergy is aimed at addressing topical avoidance, ingestion of low nickel diets (LND), and legislative change here in the USA to decrease nickel release of products coming to contact with the skin.

As nickel is very common place in foods, it is easily ingested in amounts that can cause symptoms in allergic patients. Options include the LND with or without chelation therapy. Foods rich in nickel include shellfish/seafood (tuna, herring, salmon, and mackerel), chocolate, legumes, grains (oats), nuts (almonds), and canned foods [48]. Foods (onion, garlic) and drinks (tea and coffee) should be ingested in moderation only [48]. Topical routes of nickel exposure include jewelry, coins, tools, and electronics including cell phones/lab tops.

Chelation therapy with disulfiram or tetraethyl thiuram disulfide causes chelation of nickel from the body tissue with excretion via urine mostly but also bile and sweat. In a small study of nickel allergic patients with vesicular hand eczema treated with LND and disulfiram or normal diet with placebo [76], hand eczema healed in almost all patients (10/11) on the LND with disulfiram. The addition of disulfiram with initiation of the low nickel diet increases the efficacy to as high as 90%, with two patients healing completely and eight patients with considerable improvement on 8 weeks of 100 mg twice daily of disulfiram [77]. Adverse effects to disulfiram can include hepatotoxicity, peripheral neuropathy, and optic

Table 2 SCD to foods, metals, and drugs: causative agents

	Topical non-drug induced SCD	Topical drug-induced SCD	Systemic drug-induced SCD
Foods	Aspartame		
	Balsam of Peru		
	Compositae Plants		
	(chamomile, Echinacea)		
	Garlic		
	Propylene glycol		
	Propolis		
Metals	Chromate		Gold
	Cobalt		Mercury
	Gold		
	Mercury		
	Nickel		
	Zinc		
Medications		Aminosalicyclic acid	Amoxicillin
		Ampicillin	Cephalosporins
		Anesthetics	Corticosteroids
		(benzocaine, cinchocaine)	Erythromycin
		Bufexamac	Estrogen
		Diclofenac	Ethylenediamine
		Hydroxyquinoline	Gentamycin
			Neomycin
			Nystatin

neuritis; less severe symptoms include an initial flare of the dermatitis, headache, metallic taste in the mouth, and muscle aches. Patients must not drink any alcohol while on this drug. The response rates to LND without chelation therapy are somewhat lower than LND with chelation therapy (range from 40 to 78%) and include success in children as well as adult patients [2, 61, 78]; however, in practice, LND and topical avoidance without chelation therapy is advised first as risks are negligible in comparison to disulfiram.

Strategies to attempt improving adherence to LND include a more recently proposed simplified point-based diet for patients to follow; foods are scored from 0 to 10 with 0 signifying less than 1 μg of nickel per serving and 10 with > 100 mcg of nickel per serving [79]. Adult patients are instructed to consume 15 points or less a day (150 mcg of nickel) while children are advised to consume no more than 10 points a day (100 mcg of nickel).

Other measures related to food and cooking include avoiding canned foods, using stainless steel cookware (ceramics or glass can be used as alternatives) especially with acidic foods, running tap water for a few seconds prior to using for washing, drinking, or cooking to flush out nickel from pipes, and eating iron rich foods as it competes with nickel for absorption [48, 80].

Table 3 Low chromium diet [82]

Sharma guidelines for following a low chromium diet	
1. Avoid foods that are high in chromium content such as potatoes, whole grains, legumes, yeast, nuts, and black pepper. Avoid all canned food	6. Low chromium foods include cereals, flour, refined sugars and milk are low in chromium.
2. Avoid drinks containing chromium and dietary supplements like chromium picolinate, chromium polynicotinate, chromium chloride, and chromium-enriched yeast.	7. Most vegetables are low in chromium and can be regularly consumed. Potatoes, garlic and tomatoes tend to have higher levels of chromium and should be used in moderation.
3. Acidic food should not be cooked in stainless steel as the acids may lead to the dissociation of chromium, thus increasing the chromium content of the food. Instead, consider using aluminum products.	8. Fresh fruits are generally low in chromium except for grapes, oranges, apples, bananas, which should be consumed in moderation.
4. Meat typically contains higher concentrations of chromium compared to plant based foods.	9. Tea and coffee are better avoided or consumed in moderation.
5. Simple sugars are low in chromium and also increase chromium excretion from the body through usrine.	10. Hard tap water contains high amount of chromium and should be avoided.

An initiative similar to the EU directive for low nickel content has been endorsed by national allergy and dermatology societies (ACAAI, AAAAI, ACDS) and currently a voluntary standard has been endorsed by the American Society for Testing and Materials (F2923-11) for children's jewelry with poor compliance from industry.

Other Dietary Avoidance

BOP: As noted above, BOP is chemically related to fragrances and is considered a marker for fragrance allergy. For some patients allergic to BOP, external avoidance of fragrance is not enough to eliminate their dermatitis. A diet avoiding foods containing allergens related to BOP demonstrated significant improvement [81]; however, this study was limited by a small sample size. The BOP elimination diet is challenging as many of the commonly consumed foods/drinks, mentioned in section titled "Food Induced," must be avoided.

Chromium: A low chromate diet is similarly challenging given its prevalence in many dietary items, and the fact that it is an essential element required for normal carbohydrate and lipid metabolism. The careful selection of food with relatively low concentration can bring a reduction in the total dietary intake of chromium per day. In 2009, Sharma [82] recommended a set of nine guidelines when preparing a low chromium diet, listed below in Table 3.

Adapted from: Sharma AD. Low chromate diet in dermatology. Indian J Dermatol. 2009;54(3):293–295.

Cobalt In 2008, Stuckert and Nedorost [83] proposed that a low-cobalt-diet reduced dyshidrotic eczema flares in cobalt allergic patients. They recommended a point-based diet that would help patients limit cobalt ingestion to < 12 μg per day, a level below that which will cause a flare in most patients.

Propylene Glycol In 2012, Scheman et al. [64] outlined a propylene glycol avoidance diet, by avoiding foods in categories including drinks, break products, breakfast foods, dessert/snack foods, fast foods, seafood, meat products, dairy products, prepared meals, and soups and providing alternatives.

Aspartame The artificial sweetener that metabolizes to formic acid (formaldehyde derivative) is found in numerous food products. In the paper by Scheman et al. [64], an aspartame avoidance diet was outlined. In addition to being used in many foods, it is also found in OTC medicines including Metamucil® fiber laxative and flavored supplements.

Conclusions

Systemic contact dermatitis is rare but should be considered in special populations; it is seen in context of reactions to foods, metals, and medications. The exact pathophysiology underlying this disease remains unknown, although it appears to be mediated by a type 4 hypersensitivity reaction and possibly a type 3 hypersensitivity reaction. More recently, the p-I concept has been thought to explain why SCD can be seen on first exposure to medications.

Patch testing remains the gold standard for diagnosis. The mainstay of treatment is avoidance of the medication, or dietary avoidance of the allergen (metal or food). Future studies are needed to further clarify underlying pathophysiology and to evaluate efficacy of food avoidance diets.

Compliance with Ethical Standards

Conflicts of Interest Dr. Marcella Aquino is immediate past president and a board member of the Long Island Allergy & Asthma Society; she has served as principal investigator on asthma clinical trials for Merck & Co. (SPIRO) and F. Hoffmann-La Roche (Study 1159871); has served as a sub-investigator on clinical trials for Novartis, Genentech, Shire, and Regeneron; has been paid for giving lectures by the ACAAI and WAO; has had travel expenses covered/reimbursed for travel to meetings by the ACAAI and WAO.

Dr. Gregory Rosner declares that he has no conflict of interest.

Ethical Approval and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Winnicki M, Shear NH (2011) A systematic approach to systemic contact dermatitis and symmetric drug-related intertriginous and flexural exanthema (SDRIFE): a closer look at these conditions and an approach to intertriginous eruptions. Am J Clin Dermatol 12(3):171–180
2. Veien NK (2011) Systemic contact dermatitis. Int J Dermatol 50(12):1445–1456
3. Kaaber K, Sjolin KE, Menne T (1983) Elbow eruptions in nickel and chromate dermatitis. Contact Dermatitis 9(3):213–216
4. Fabbro SK, Zirwas MJ (2014) Systemic contact dermatitis to foods: nickel, BOP, and more. Curr Allergy Asthma Rep 14:463
5. Menne T et al (1994) Systemic contact dermatitis. Am J Contact Dermat 5:1–12
6. Andersen KE, Hjorth N, Menne T (1984) The baboon syndrome: systemically-induced allergic contact dermatitis. Contact Dermatitis 10(2):97–100
7. Gawkrodger DJ, McVittie E, Hunter JA (1987) Immunophenotyping of the eczematous flare-up reaction in a nickel-sensitive subject. Dermatologica 175(4):171–177
8. Di Gioacchino M et al (1995) Immuno-histopathologic changes in the gastrointestinal mucosa in patients with nickel contact allergy. G Ital Med Lav 17(1–6):33–36
9. Boscolo P, Andreassi M, Sabbioni E, Reale M, Conti P, Amerio P, di Gioacchino M (1999) Systemic effects of ingested nickel on the

immune system of nickel sensitised women. Life Sci 64(17):1485–1491
10. Di Gioacchino M et al (2000) Lymphocyte subset changes in blood and gastrointestinal mucosa after oral nickel challenge in nickel-sensitized women. Contact Dermatitis 43(4):206–211
11. Roychowdhury S, Svensson CK (2005) Mechanisms of drug-induced delayed-type hypersensitivity reactions in the skin. AAPS J 7(4):E834–E846
12. Jensen CS, Lisby S, Larsen JK, Veien NK, Menne T (2004) Characterization of lymphocyte subpopulations and cytokine profiles in peripheral blood of nickel-sensitive individuals with systemic contact dermatitis after oral nickel exposure. Contact Dermatitis 50(1):31–38
13. Posadas SJ, Pichler WJ (2007) Delayed drug hypersensitivity reactions - new concepts. Clin Exp Allergy 37(7):989–999
14. Lachapelle JM The Spectrum of diseases for which patch testing is recommended. In: *Patch Testing & Prick Testing: A Practical Guide Official Publication of the ICDRG*, springer-Verlag, editor. 2009. Springer Berlin Heidelberg, Berlin, pp 7–31
15. Hausermann P, Harr T, Bircher AJ (2004) Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Dermatitis 51(5–6):297–310
16. Ozkaya E (2014) Current understanding of baboon syndrome. Expert Rev Dermatol 4(2):163–175
17. Miyahara A, Kawashima H, Okubo Y, Hoshika A (2011) A new proposal for a clinical-oriented subclassification of baboon syndrome and a review of baboon syndrome. Asian Pac J Allergy Immunol 29:150–160
18. Veien NK, Christiansen AH, Svejgaard E, Kaaber K (1979) Antibodies against nickel-albumin in rabbits and man. Contact Dermatitis 5(6):378–382
19. Polak L, Turk JL (1968) Studies on the effect of systemic administration of sensitizers in Guinea-pigs with contact sensitivity to inorganic metal compounds. I. The induction of immunological unresponsiveness in already sensitized animals. Clin Exp Immunol 3(3): 245–251
20. Tan S-C, Tan JW-l (2011) Symmetrical drug related intertriginous and flexural exanthema. Curr Opin Allergy Clin Immunol 11:313–318
21. Gallo R, Parodi A (2002) Baboon syndrome from 5-aminosalicyclic acid. Contact Dermatitis 46(2):110
22. Nakada T, Matsuzawa Y, Matsuzawa Y (2012) Allergic Contact Dermatitis Syndrome From Bufexamac for Nursing Infant. Dermatitis 23(4):185–186
23. Proske S, Uter W, Schnuch A, Hartschuh W (2003) Severe allergic contact dermatitis with generalized spread due to bufexamac presenting as the "baboon" syndrome. Dtsch Med Wochenschr 128(11):545–547
24. European Medicines Agency recommends revocation of marketing authorisations for bufexamac. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/04/WC500089623.pdf#search='eu,%20bufexamac'
25. Lakshmi C, Srinivas C (2011) Systemic (allergic) contact dermatitis to diclofenac. Indian J Dermatol Venereol Leprol 77(4):536
26. Rajan JP, Cornell R, White AA (2015) A case of systemic contact dermatitis secondary to edetate disodium. J Allergy Clin Immunol Pract 3(4):607–608
27. Mussani F, Poon D, Skotnicki-Grant S (2013) Systemic contact dermatitis to topical clioquinol/hydrocortisone combination cream. Dermatitis 24(4):196–197
28. Oliveira A, Rosmaninho A, Lobo I, Selores M (2011) Intertriginous and flexural exanthema after application of a topical anesthetic cream: a case of baboon syndrome. Dermatitis 22(6):360–362
29. Erdmann S, Sachs B, Merk H (2001) Systemic contact dermatitis from cinchocaine. Contact Dermatitis 44(4):260261
30. Malinauskiene L, Isaksson M, Bruze M (2013) Systemic contact dermatitis in a gold-allergic patient after treatment with an oral homeopathic drug. J Am Acad Dermatol 68(2):e58
31. Moller H et al (1996) Flare up at contact allergy sites in a gold treated rheumatic patient. Acta Derm Venerol 76(1):55–58
32. Klein-Gitelman MS, Pachman LM (1998) Intravenous corticosteroids: adverse reactions are more variable than expected in children. J Rheumatol 25(10):1995–2002
33. Baeck M, Goossens A (2012) Systemic contact dermatitis to corticosteroids. Allergy 67(12):1580–1585
34. Barbaud A, Waton J (2016) Systemic allergy to corticosteroids: clinical features and cross reactivity. Curr Pharm Des 22(45): 6825–6831
35. Garcia-Bravo B, Repiso JB, Camacho F (2000) Systemic Contact Dermatitis to Deflazacort. Contact Derm **43**:359–360
36. Bianchi L, Hansel K, Antonelli E, Bellini V, Rigano L, Stingeni L (2016) Deflazacort hypersensitivity: a difficult-to-manage case of systemic allergic dermatitis and literature review. Contact Dermatitis 75(1):54–56
37. Treudler R, Simon J (2006) Symmetric, drug-related, intertriginous, and flexural exanthema in a patient with polyvalent intolerance to corticosteroids. J Allergy Clin Immunol 118:965–967
38. DeKoven JG, Warshaw EM, Belsito DV, Sasseville D, Maibach HI, Taylor JS, Marks JG, Fowler JF Jr, Mathias CGT, DeLeo VA, Pratt MD, Zirwas MJ, Zug KA (2017) North American contact dermatitis group patch test results 2013-2014. Dermatitis 28(1):33–46
39. Guin JD, Phillips D (1989) Erythroderma from systemic contact dermatitis: a complication of systemic gentamicin in a patient with contact allergy to neomycin. Cutis 43(6):564–567
40. Haeberle M, Wittner B (2009) Is gentamicin-loaded bone cement a risk factor for developing systemic allergic dermatitis? Contact Dermatitis 60:176–177
41. Wolf R, Orion E, Matz H (2003) The baboon syndrome or intertriginous drug eruption: a report of eleven cases and a second look at its pathomechanism. Dermatol Online J **9**(3):2
42. Goossens C, Sass U, Song M (1997) Baboon syndrome. Dermatology 194:421–422
43. Wolf R, Elman M, Brenner S (1993) Drug-induced "intertrigo". Int J Dermatol 32(7):515–516
44. Ash S, Scheman AJ (1997) Systemic contact dermatitis to hydroxyzine. Am J Contact Dermat 8(1):2–5
45. Cusano F, Ferrara G, Crisman G, Sarracco G, Zalaudek I, Argenziano G (2006) Clinicopathologic features of systemic contact dermatitis from ethylenediamine in cetrizine and levocetrizine. Dermatology 213(4):353–355
46. Isaksson M, Ljunggren B (2003) Systemic contact dermatitis from ethylenediamine in an aminophylline preparation presenting as the baboon syndrome. Acta Derm Venereol 83(1):69–70
47. Walker S, Ferguson S (2004) Systemic allergic contact dermatitis due to ethylenediamine following administration of oral aminophylline. Br J Dermatol 150(3):594
48. Sharma AD (2007) Relationship between nickel allergy and diet. Indian J Dermatol Venereol Leprol 73(5):307–312
49. Brandao MH et al (2010) Ear piercing as a risk factor for contact allergy to nickel. J Pediatr 86(2):149–154
50. Thyssen JP (2011) Nickel and cobalt allergy before and after nickel regulation–evaluation of a public health intervention. Contact Dermatitis 65(Suppl 1):1–68
51. Kulberg A, Schliemann S, Elsner P (2014) Contact dermatitis as a systemic disease. Clin Dermatol 32:414–419
52. Lerch M, Bircher AJ (2004) Systemically induced allergic exanthem from mercury. Contact Dermatitis 50(6):349–353
53. Audicana M, Bernedo N, Gonzalez I, Munoz D, Fernandez E, Gastaminza G (2001) An unusual case of baboon syndrome due to mercury present in a homeopathic medicine. Contact Dermatitis 45(3):185

54. Shimizu T, Kobayashi S, Tanaka M (2003) Systemic contact dermatitis to zinc in dental fillings. Clin Exp Dermatol 28(676):675
55. Saito N, Yamane N, Matsumura W, Fujita Y, Inokuma D, Kuroshima SI, Hamasaka K, Shimizu H (2010) Generalized exacerbation of systemic allergic dermatitis due to zinc patch test and dental treatments. Contact Dermatitis 62(6):372–373
56. Pigatto PD, Guzzi G (2004) Systemic contact dermatitis from nickel associated with orthodontic appliances. Contact Dermatitis 50(2): 100–101
57. Hausen BM et al (1995) Identification of new allergenic constituents and proof of evidence for coniferyl benzoate in balsam of Peru. Am J Contact Dermatitis 6(4):199–208
58. Belsito DV (2001) Surviving on a balsam-restricted diet: cruel and unusual punishment or medically necessary therapy? J Am Acad Dermatol 45(3):470–472
59. Hill AM, Belsito DV (2003) Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame? Contact Dermatitis 49(5):258–259
60. Nijhawan RI et al (2009) *Systemic contact dermatitis*. Dermatol Clin **27**(3):355–364 vii
61. Matiz C, Jacob SE (2011) Systemic contact dermatitis in children: how an avoidance diet can make a difference. Pediatr Dermatol 28(4):368–374
62. Dejobert Y, Delaporte E, Piette F, Thomas P (2001) Vesicular eczema and systemic contact dermatitis from sorbic acid. Contact Dermatitis 45(5):291
63. Giordano-Labadie F, Pech-Ormieres C, Bazex J (1996) Systemic contact dermatitis from sorbic acid. Contact Dermatitis 34(1):61–62
64. Scheman A, Cha C, Jacob SE, Nedorost S (2012) Food avoidance diets for systemic, lip, and oral contact allergy: an american contact alternatives group article. Dermatitis 23(6):248–257
65. Burden AD, Wilkinson SM, Beck MH, Chalmers RJG (1994) Garlic-induced systemic contact dermatitis. Contact Dermatitis 30(5):299–300
66. Veien NK (1997) Ingested food in systemic allergic contact dermatitis. Clin Dermatol 15(4):547–555
67. Cho E, Lee JD, Cho SH (2011) Systemic contact dermatitis from propolis ingestion. Ann Dermatol 23(1):85–88
68. Jacob SE, Scheman A, McGowan MA (2017) Allergen of the year: propylene glycol. Dermatitis 29(1):3–5
69. Warshaw EM, Botto NC, Zug KA, Belsito DV, Maibach HI, Sasseville D, Fowler JF Jr, Storrs FJ, Taylor JS, DeLeo V, Marks JG Jr, Mathias CG, Pratt MD, Rietschel RL (2008) Contact dermatitis associated with food: retrospective cross-sectional analysis of north American contact dermatitis group data, 2001-2004. Dermatitis 19(5):252–260
70. Lowther A, McCormick T, Nedorost S (2008) Systemic contact dermatitis from propylene glycol. Dermatitis 19(2):105–108
71. Pereira F, Santos R, Pereira A (1997) Contact dermatitis from chamomile tea. Contact Dermatitis 36(6):307
72. Rodriguez-Serna M, Sanchez-Motilla JM, Ramon R, Aliaga A (1998) Allergic and systemic contact dermatitis from Matricaria chamomilla tea. Contact Dermatitis 39(4):192–193
73. Rycroft RJ (2003) Recurrent facial dermatitis from chamomile tea. Contact Dermatitis 48(4):229
74. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A, European Society of Contact Dermatitis (2001) Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis 45(6):321–328
75. Brockow K et al (2002) General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 57(1):45–51
76. Sharma AD (2006) Disulfiram and low nickel diet in the management of hand eczema: a clinical study. Indian J Dermatol Venereol Leprol 72(2):113–118
77. Christensen OB, Kristensen M (1982) Treatment with disulfiram in chronic nickel hand dermatitis. Contact Dermatitis 8(1):59–63
78. Veien NK, Hattel T, Laurberg G (1993) Low nickel diet: an open, prospective trial. J Am Acad Dermatol 29(6):1002–1007
79. Mislankar M, Zirwas MJ (2013) Low-nickel diet scoring system for systemic nickel allergy. Dermatitis 24(4):190–195
80. Joneja JM (1995) Specific food restrictions nickel allergy. In: Managing food allergy & intolerance: a practical guide. J.A. Hall Publications, Port Coquitlam (BC), pp 247–262
81. Salam TN, Fowler JF Jr (2001) Balsam-related systemic contact dermatitis. J Am Acad Dermatol 45(3):377–381
82. Sharma AD (2009) Low chromate diet in dermatology. Indian J Dermatol 54(3):293–295
83. Stuckert J, Nedorost S (2008) Low-cobalt diet for dyshidrotic eczema patients. Contact Dermatitis 59(6):361–365