



Systemic Contact Dermatitis: The Routes of Allergen Entry

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Accepted: 28 June 2021

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Abstract

Systemic contact dermatitis (SCD) is a generalized reactivation of type IV hypersensitivity skin diseases in individuals with previous sensitization after a contact allergen is administered systemically. Patients with SCD may consider their dermatitis unpredictable and recalcitrant since the causative allergens are difficult to find. If a patient has a pattern of dermatitis suggestive of SCD but fails to improve with conventional treatment, SCD should be taken into consideration. If doctors are not familiar with the presentations of SCD and the possible routes of allergen sensitization and exposure, the diagnosis of SCD may be delayed. In this work, we summarized all of the routes through which allergens can enter the body and cause SCD, including oral intake, local contact (through skin, inhalation, nasal spray and anal application), implants, and other iatrogenic or invasive routes (intravenous, intramuscular, intraarticular, and intravesicular). This will provide a comprehensive reference for the clinicians to identify the culprit of SCD.

Keywords Systemic contact dermatitis · Baboon syndrome · Oral intake · Inhalation · Iatrogenic · Implants

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Introduction

Systemic contact dermatitis (SCD) is a generalized reactivation of skin diseases in individuals with skin sensitization after a contact allergen is administered systemically [1–3]. In SCD, allergens spread hematogenously. Compared with contact dermatitis, the prevalence of SCD is very low. SCD has several clinical reaction patterns, including flare-up of previous exposure sites (previous dermatitis or patch test sites), vesicular hand dermatitis, flexural dermatitis, Baboon syndrome (BS), exfoliative erythema, vasculitis-like lesions, and widespread maculopapular dermatitis [1, 4–6]. In addition, cases of SCD presenting as acute generalized exanthematous pustulosis (AGEP) [7] or palmoplantar pustulosis have been reported [8, 9]. Systemic symptoms, including headaches, nausea, vomiting, fever, malaise, arthralgia, and diarrhea, may be present [1, 4, 10].

SCD was thought to be a type IV hypersensitivity reaction, and the pathogenetic mechanism of SCD was similar to that of local contact dermatitis [1]. The allergens are taken up in the skin by antigen-presenting cells, which then migrate to local lymph nodes and stimulate the proliferation of T cells. After that, the effector T

lymphocytes return to the skin and cause skin damage [11]. In SCD, different from contact dermatitis, allergens spread hematogenously rather than stay in the local skin. In patients with SCD, the memory T lymphocytes circulating in the blood encounter allergens and then migrate to the skin [12]. The characteristic affected skin areas of baboon syndrome were areas with abundant sweat glands. Therefore, it was suggested that allergens were discharged through sweat glands and then caused the local dermatitis [13]. In some cases, type III [14] and type I hypersensitivity [15] reactions were also suggested to be involved, but the evidence was limited.

Patients with SCD may consider their dermatitis unpredictable since the causative allergens are difficult to find. If a patient has a pattern of dermatitis suggestive of SCD but fails to improve with conventional treatment, SCD should be taken into consideration. A detailed medical history should be taken, focusing on possible routes of allergen entry (Fig. 1). Occasionally, the allergens can enter the body and cause SCD through more than one route [16, 17]. Patch test to suspicious allergens should be performed. The timely recognition of SCD is critical to preventing more severe symptoms.

In this work, we summarized all of the routes through which allergens can enter the body and cause SCD, including oral intake, implants, and other iatrogenic or invasive routes (intravenous, intramuscular, intraarticular and intravesicular) and local contact (through skin, inhalation, nasal spray and anal application) (Fig. 1).

The Routes of Allergen Entry

Oral Intake

Ingestion is an important route of allergen entry. However, systemic contact dermatitis caused by ingestion is probably underrecognized. Patients often fail to realize that the food contains contact allergens. Oral routes can occur with food, supplements, oral medications, and other ingested materials (Fig. 2).

Food

Botanicals The representing allergens that are extensively reported are balsam of Peru (BOP), garlic, propolis, compositae, and cashew nuts. BOP, a natural extract from the *Myroxylon pereirae* tree, is a common flavor in many food and drinks [16]. It has been extensively reported as a cause of SCD [18]. Dietary avoidance of BOP significantly benefits patients at risk for SCD [16, 19]. Garlic has been implicated in several cases of SCD, manifesting as a chronic vesicular hand eczema [20] or generalized skin eruption [21]. Propolis has been reported to cause eruptions of SCD in several cases via oral intake of propolis capsules or propolis syrup [22, 23]. Compositae has been recognized as a dietary cause of SCD via drinking chamomile tea or intake of other products of the Compositae family [24–28]. Contact sensitization via exposure to Rhus lacquer polished furniture is relatively common in east Asia [29]. The chief antigenic component

Fig. 1 Routes of allergen entry

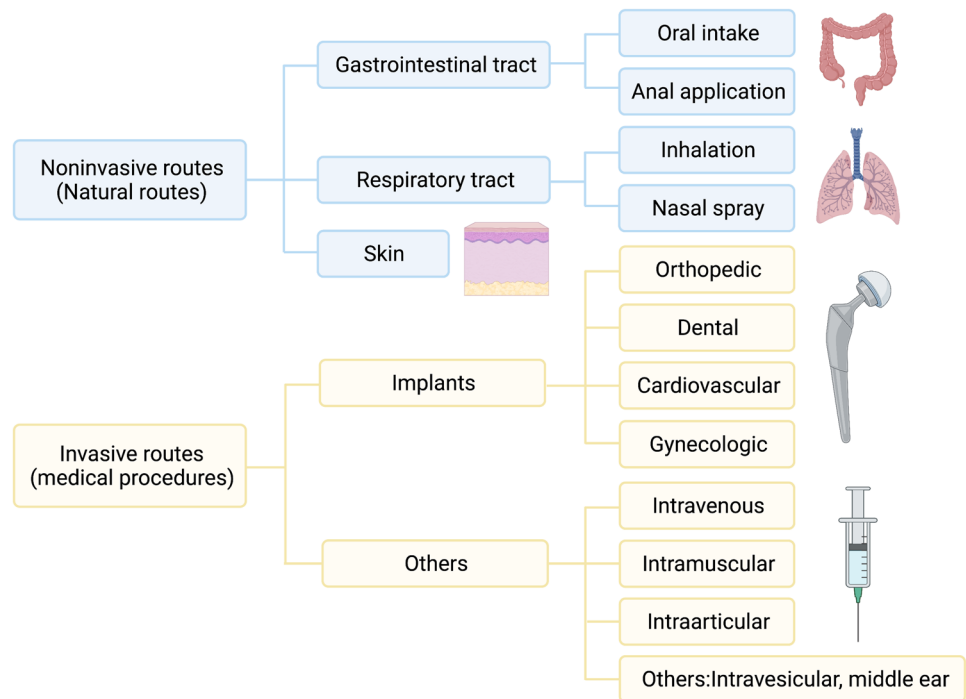
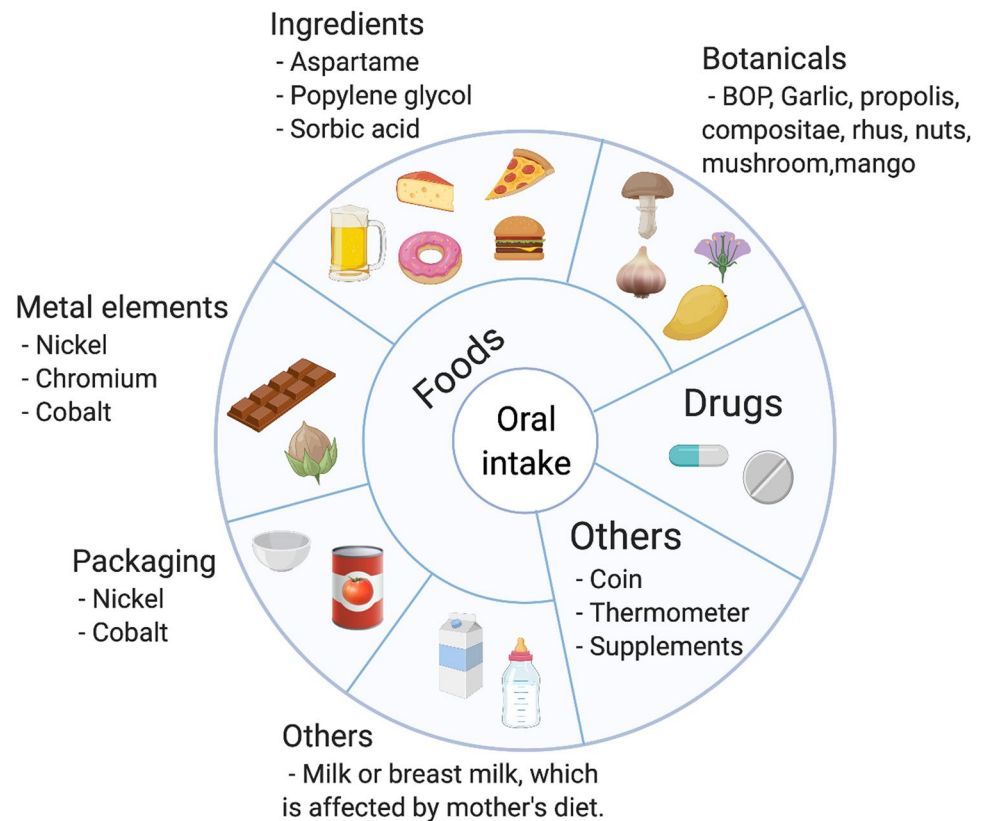


Fig. 2 Allergens which cause SCD through oral intake



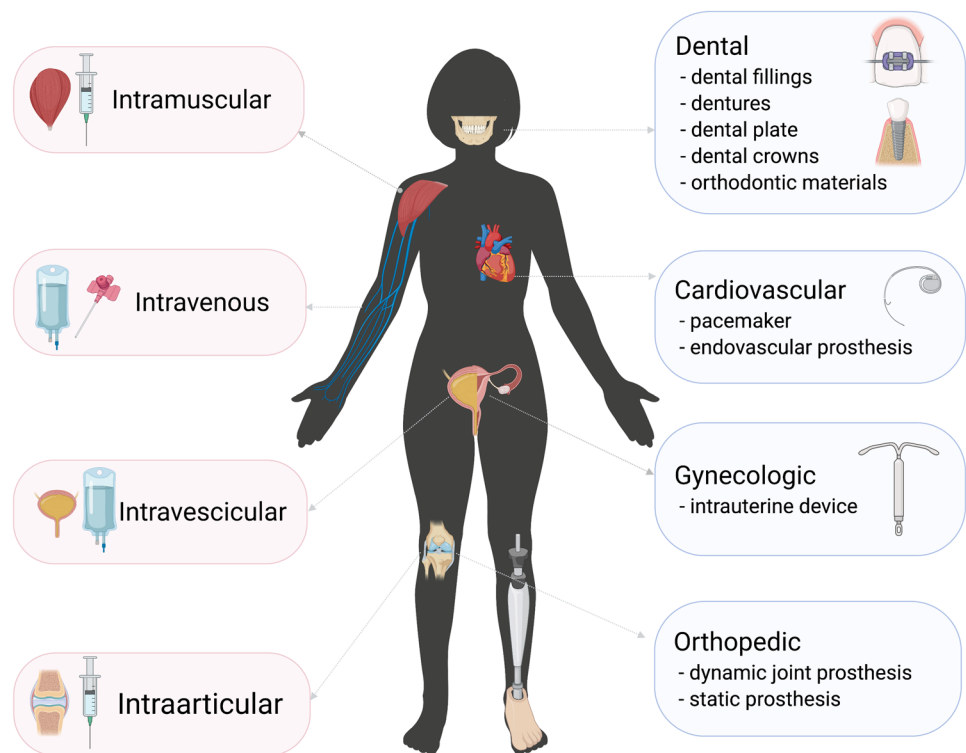
in Rhus is urushiol [29]. SCD occurrence after oral intake of rhus-related foods (such as Rhus Chicken) [30, 31] or herbal remedies [32, 33] has been frequently reported. Exposure to cashew nuts may elicit generalized skin eruptions in poison ivy-sensitized patients [34, 35]. Both rhus and cashew nuts belong to the *Anacardiaceae* family and share similar allergens that cross-react immunologically [35]. Consumption of other plants, such as mango flesh [36] and raw shiitake mushroom [37], has also been reported to elicit SCD.

Food Additives/Ingredients Propylene glycol, sorbic acid/sorbates, and aspartame are examples of food ingredients that cause SCD [38]. Aspartame is a popular artificial sweetener. It is metabolized into formaldehyde in the body and thus may cause SCD in formaldehyde-sensitive patients [39]. Propylene glycol, named the American Contact Dermatitis Society's Allergen of the Year for 2018, is widely used in food and cosmetics [1, 38, 40]. A meal containing PG would cause flares of contact dermatitis in a patient who was allergic to PG [41]. Sorbic acid is present naturally in some fruits and is also used as a preservative in foods or other products [38, 42]. Patients can become sensitized to sorbic acid through cutaneous use of creams and developed generalized eczema through oral intake of sorbic-containing foods such as cranberries, strawberries, margarine, currants and prunes [42, 43]. Food avoidance for SCD caused by the

aforementioned food additives has been proposed in several articles [1, 3, 16, 38]. Oral administration of small amounts of butylated hydroxyanisole and butylated hydroxytoluene, used as antioxidants in food, can elicit acute flares of vesicular eczema of the fingers [44].

Trace Metal Elements Elemental metal in food and water are important causes of SCD in a dose-dependent manner. Elemental metals, such as nickel, cobalt, chromium, and zinc, are ubiquitous in many foods, but patients suffering from metal induced SCD may be unaware that metals in food can be the cause of their often recalcitrant dermatitis. Nickel is considered the most common ingestible contact allergen [3]. Foods that contained high level of elemental metals are reviewed in several articles [1, 3, 16]. A 46-year-old woman presented with an 8-month history of foot dermatitis after taking flaxseed supplements in the preceding months [45]. Patch testing revealed positive reactions to nickel and cobalt, both of which are contained in flaxseed in high quantities. The dermatitis resolved completely after she avoided foods that contained high levels of nickel and/or cobalt, especially flaxseed [45]. Similarly, a meal containing cobalt and/or palladium caused recurrent eczematous lesions in a 26-year-old woman, who had a positive patch test result to cobalt and palladium [46]. A 14-year-old boy developed recurrent disseminated dermatitis 1 day

Fig. 3 Iatrogenic invasive routes causing SCD. The blue blocks represent the implants reported to cause SCD. The red blocks represent other iatrogenic invasive routes that may cause SCD



following ingestion of a chocolate-containing diet, and his patch test showed positive reactions to nickel [47]. Low-nickel, low-cobalt, low-chromium, or low-zinc diets are effective ways to treat SCD in nickel, cobalt, chromium, or zinc-sensitized individuals [3, 16, 48, 49].

Food Packaging The packaging of food may also be an unrecognized source of allergens. Canned food contains high levels of nickel due to the packaging [16]. Thus, it is recommended that canned food be avoided in nickel-allergic patients.

Others Since breast milk is affected by the diet of the mother, contact allergens transferred into the milk can cause SCD in an allergic infant. In one case report, an infant suffering from pompholyx for several months was found to be allergic to chromium. His mother consumed large quantities of high-chromium-containing chocolate and cocoa daily [50]. Similarly, as early as 60 years ago, it was reported that penicillin, which was fed to cows, was secreted in cow's milk and led to a dermatitis of the face and arms of a 54-year-old man [51].

Medicaments

Dozens of oral drugs have been reported to cause SCD [1, 40, 52, 53]. These include antibiotics and antifungals,

anesthetics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), biological agents, antineoplastic drugs, radiocontrast, psychopharmaceuticals, and others [1, 40, 52–54]. Many cases of SCD present as BS or symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) [55]. The drugs which have been reported to cause SCD are listed in Table 1.

Metals contained in some medicaments can cause SCD. A gold-allergic patient developed a macular and popular eruption after treatment with an oral homeopathic medication, Aurocard [56]. Mercury is a quite common cause of Baboon syndrome. Mercurial in a lozenge for pharyngitis caused an acute itchy exanthem in an 8-year-old boy who has a history of mercurial allergy [57]. A patient allergic to dichromate developed severe exacerbations of eczema after taking a homeopathic drug containing chromium [58].

Similarly to food additives, drugs additives can also cause SCD in sensitized patients. In a case reported by Matiz and Jacob [16], generalized erythema and eyelid dermatitis of an 11-year-old boy improved with discontinuation of his Montelukast chewable tablets. He was not contact sensitized to montelukast, but to the aspartame contained in the chewable tablets [16].

Others

Supplements Components in nutritional supplements are also sources of allergens that cause SCD. Chromium picolinate

Table 1 The comparison of routes and allergens that cause systemic contact dermatitis

Routes																
	Food	Oral intake/ingestion	Oral drugs	Others	Orthopedic	Dental	Implants	Cardiovascular	Gynecologic	I.V.	Other invasive routes	Others	Skin	Local contact	Intrarectal	
Metals	Nickel	Flaxseed[45], Chocolate[136]		Coins [63]	[5, 91, 94, 99, 101]	[102-105]	[114, 117-119]			L.V. Cannulas [130, 131], Dialysis system [132]						
	Chromium	Mother's milk [50]	[58]	Supplements [59-61]	[94, 95, 98]	[107]						Acupuncture [15]		Welding fumes [73, 74]		
	Cobalt	[46], Flaxseed [45]		Vitamin B12 [62]	[5, 91, 96, 97, 99]	[102]						Acupuncture [15]	Leather[16]	Hard-metal work [75]		
	Mercury		Lozenge [57]	[65]									Thermometer[13]	[76]		
	Zinc	[49]				[92]										
	Titanium															
	Gold		[56]								[133]					
	Palladium	[46]				[91]										
	Molybdenum															
	Copper															
Allergen Medications	Anesthetics		Codeine[137]							IUD [9, 120-125]						
	Antibiotics and antifungals	Penicillin in milk [51]	Amoxicillin[8] Ampicillin [38] Clindamycin [139] Erythromycin [140] Isoniazid [141] Metronidazole [139] Miconazole [142] Nystatin[143] Neomycin [4, 144] Rosythromycin [145] Terbinafine [146]		Gentamicin [93]					Amoxicillin [147]		Ampicillin in middle ear [135]	Gentamicin [10] Erythromycin [70] Metronidazole suppository [72]		Cinchocaine[81-83], Tetracaine [84, 85]	
	Corticosteroids		Betamethasone [148] Cloprednol [148] Deflazacort [71, 148] Dexamethasone[71, 148, 149] Hydrocortisone[71, 148] Methylprednisolone[126, 148] Prednisolone[71, 148] Methyl salicylate[150] Diclofenac [151]							Methylprednisolone [126] Hydrocortisone [126]	Betamet/Betamethasone [126] hasone Methylprednisolone [7, 126] [126] Triamcinolone acetone[126]		Hydrocortisone [71] Budesonide [78, 79] budesonide [71]			
	NSAIDs															
	Biological agents															
	Antineoplastic									Cetuximab [152] IVIg [153] Fluorouracil [154]						
	Psychopharmac		Risperidone [155] Phenobarbital [156] Lofazepate ethyl [157] Clonazepam [158]													
	Others		Amlexanox [17] Hydroxyurea [159] Cimetidine [160] Methoxypropisalen [161] Pseudoephedrine [162, 163] Disulfiram [164] Valacyclovir [165] Vitamin B6 [166]							EDTA [127-129] Radiocontrast media (Iomeprol, Iopromide) [167]			Estradiol [168] Resorcinol [67] Vitamin B6 [166]			
	BOP	[18, 19]														
	Botanicals	Garlic	[20, 21]													
Propolis		[22, 23]														
Compositae		[24-28]														
Rhus related		[30-33]														
cashew nuts		[34, 35]														
others		[36]														
Mango flesh		[36]														
Mushroom		[37]														
Propylene glycol		[41]														
Sorbic acid		[38, 42, 43]														
Other	Aspartame		Formaldehyde [39]	Montelukast [16]												
	silicone															
	epoxy resin															
	Edetate disodium															
	antioxidants															
Cosmetics	Butylated hydroxyanisole	[44]														
Nails																
Nose																
Eyes																
Ears																
Mouth																
Vagina																
Rectum																
Anus																
Skin																
Nails																
Eyes																
Ears																
Mouth																
Vagina																

[59] and chromium chloride in multivitamin tablets [60] or in syrup [61] can trigger generalized dermatitis in individuals who were allergic to chromium. Vitamin B12 supplement, of which cobalt is an essential element, resulted in pigmented systemic contact dermatitis in a 55-year-old female [62].

Theoretically, any foreign objects swallowed can cause SCD in individuals who are allergic to the allergens in the item. There was an interesting case report in which a nickel-allergic patient suffered a pompholyx-like dermatitis on her hands and arms only 24 h after she swallowed a nickel-containing coin [63]. A similar case of nickel dermatitis after coin ingestion was reported in an 8-year-old girl [64]. A 41-year-old female who accidentally ingested a tiny amount of mercury from thermometer developed typical dermatitis of Baboon syndrome. Patch test results at day 4 showed + + reactions to mercury [65].

Local Contact

Skin and Mucosa

Typically, skin contact with allergens only causes local contact dermatitis in sensitized patients. In rare cases, the trace amount of allergen absorbed by skin is enough to elicit a systemic eruption. For example, the phenomenon

in which a patient’s previous lesions flares dramatically during patch testing is evidence of skin contact–induced SCD [10, 24, 66, 67]. Skin contact with leather goods, which contain nickel and/or cobalt, can elicit generalized dermatitis in some people [16]. A teenager starting to use razor presented with eczematoid plaques on thighs and trunk. Patch test indicated that nickel in the razor was the cause [16].

Local use of skin cream, which contained drugs such as hydrocortisone, budesonide, buprenorphine, gentamicin, or erythromycin, has been reported to cause SCD in several patients [10, 68–71]. When the skin is wounded, it is possible that allergens get into the body more easily [10].

Contact with vagina mucosa can elicit SCD. Metronidazole suppository was reported to induce SCD in a patient [72].

Inhalation and Nasal Spray

Allergen entry through respiratory tract is also a rare and unusual cause of SCD. The routes include inhalation and nasal spray.

Metals Inhalation of chromium from welding fumes [73, 74] or cobalt from hard-metal work [75] caused generalized

eczematous eruption in several cases. An accident inhalation of mercury elicited Baboon syndrome in a 25-year-old man [76]. Inhalation of mercury spillage from a broken mercury thermometer elicited Baboon syndrome in a 31-year-old woman [13].

Botanicals BOP, as a common component in perfumes, can also cause SCD through inhalation [16]. A 35-year-old male suffering a widespread rash with summer exacerbation was suspected of having SCD caused by inhalation of plant parts of *Parthenium hysterophorus*. His patch test was positive to aqueous extract of *P. hysterophorus*. Exposure to fresh *P. hysterophorus* materials via inhalation from a polythene bag also elicited an exacerbation of dermatitis and pruritus [77].

Drugs Inhaled budesonide can cause cutaneous reactions in patients with delayed corticosteroid hypersensitivity [78, 79]. The administration of antigen nasally can also trigger systemic symptoms. Edetate disodium in azelastine nasal spray has been shown to be the culprit in a case of SCD [80].

Anal Application

Anal application of anesthetics-containing ointment is often used for the treatment of hemorrhoids or in rectal examination. The anesthetic components of the cream, such as cinchocaine and tetracaine, were reported to elicit systemic contact dermatitis in several cases [81–85]. Non-steroidal anti-inflammatory drugs (NSAIDs), such as 5-aminosalicylic acid and bufenacemac, are also often used in foam enemas and were reported to cause SCD in several cases [86, 87].

Implants

Although more and more biocompatible materials are being used in the production of implants, SCD due to the allergens in implants still occurs (Fig. 3). The implants have constant contact with human tissues and continuously release trace amounts of allergens, which can elicit allergic reactions in patients. Conversely, patients with known sensitization to metals before the implantation did not always suffer from systemic dermatitis or other allergic reactions [88, 89]. In a prospective study, only five out of 24 patients (19.2%) who displayed preoperative responses to at least one metal suffered from SCD after the implantation [89].

Orthopedic Implants

Among the implants that cause SCD, orthopedic implants are the most common type and are often made from stainless steel, metal alloys, or titanium [90]. The most important allergens in orthopedic implants are metals, such as nickel, cobalt, and chromium, and less commonly palladium and

titanium [91, 92]. Besides metals, methyl methacrylate and antibiotics in the implants can also cause SCD [93]. In most cases, the dermatitis originated from the site near implantation and then became generalized. A few cases presented as eczema on hands [94]. Orthopedic implants can be classified into static implants and dynamic joint implants. Compared to static implants, dynamic joint implants theoretically tend to have higher physical wear, which means a higher number of allergens released into the body.

Dynamic Joint Implants Knee arthroplasty [93, 95, 96], hip arthroplasty [97, 98], patella prosthesis [99], leg prosthesis [99], and metatarsophalangeal joint hemi implant [91] were reported to cause SCD in some patients. In a prospective study conducted by Niki and colleagues, five out of 92 patients (5.4%) who underwent total knee arthroplasty displayed implant metal-related eczema [89].

In rare cases, it was the antibiotic loaded in the bone cement, rather than metal ions, that cause the dermatitis. Haeberle M and Wittner B reported a 74-year-old female who developed generalized eczematous rash after left knee replacement [93]. The bone cements had been incorporated with gentamicin in order to reduce the chance of infections after surgery. A positive patch test reaction to gentamicin sulfate was observed [93].

Static Implants Osteosynthesis and bone plate fixation are common orthopedic procedures that involve static implants. Bone plates made from titanium [100], stainless steel [94, 101], or other metal alloys [5, 99] have been reported to cause SCD.

Dental Implants and Prosthesis

Dental implants; dental prostheses such as dentures, dental fillings, dental plate, and dental crowns; and orthodontic materials contain metals which can be released into the body and thus cause SCD. The allergens are absorbed through the oral mucosa or enter the circulation directly through osseointegration. Interestingly, most of the cases have no lesions on the oral mucosa which had direct contact with the allergens [102–104]. Considering the wide use of dental prostheses, the incidence of SCD caused by dental prosthesis is very low.

Steel and other metal alloys are often used as dental materials. In the long process of orthodontic treatment, the components of steel, such as chromium, cobalt, and nickel, can elicit vesicular dermatitis of the fingers, eyelid dermatitis, or generalized eczema in several cases [102–105]. Similarly, chromium in dental crowns [106] and dental plate [107] was discovered to be the culprit of generalized eczema in chromium-sensitive patients. In addition, there was a case report that cobalt-chromium-molybdenum alloy denture frameworks cause diffused eczema in a patient whose patch

test showed positive results for both cobalt and molybdenum [108].

Amalgam and zinc are widely used components in dental restoration. Zinc is not a very common allergen compared to other metals like nickel, chromium, and cobalt, but zinc was reported to cause generalized erythema [66, 109] and to cause palmoplantar pustulosis [8] who had zinc-containing dental fillings in a few cases. Dental amalgam was the culprit of SCD in two cases [103, 110].

Titanium rarely causes allergic reactions and thus is considered highly biocompatible. However, cases with diffused eczema or facial eczema in association with dental implants made of high-purity titanium have also been reported [111, 112].

Cardiovascular Implants

Hypersensitivity reactions to endovascular prostheses are uncommon. Among the reported cases, some patients suffered generalized eczema after receiving the implants and had a positive patch test to one or more of the components in the implant.

Pacemaker Honari G et al. summarized over 20 cases of contact sensitivity associated with pacemakers [113]. While most of the cases presented as localized dermatitis, two of the cases are pacemaker-induced SCD. A 70-year-old woman, who had a history of contact dermatitis with nickel, developed an acute pompholyx-like eruption on both hands, only 2 days after implantation of a pacemaker-containing nickel [114]. Besides metals, silicone adhesive and epoxy resin in pacemakers were also causes of SCD in two males [115, 116].

Endovascular Prosthesis Stainless steel and nitinol are often used in endovascular implants. Contact allergy to endovascular stents is believed to not only cause localized and systemic contact dermatitis but also to be possibly partially responsible for intraluminal restenosis [90]. A 79-year-old woman with an abdominal aortic aneurysm received an endoluminal repair with a straight Vanguard I endograft made of a self-expanding nitinol alloy. Three weeks later, a severe episode of erythema and eczema on the legs occurred. A positive patch test to nickel sulfate and cobalt chloride suggested that nickel in the alloy was released into the circulation and caused the eczema [117]. A 44-year-old man suffered from a severe eczematous rash over his entire body within 2 to 4 weeks after he underwent left popliteal artery stent placement [118]. Patch test was positive for nickel, which was contained in the stainless steel-made stent as well as stainless steel vascular clips. Similarly, a severe generalized dermatitis after a superficial femoral artery nitinol stent placement was reported [119]. Patch test showed the patient had a severe reaction to nickel [119].

Gynecologic Implants

Intrauterine Contraceptive Device Intrauterine devices (IUDs) often contain copper. Although hypersensitivity to copper is rare, several female patients in their reproductive age, ranging from 23 to 41 years old, were reported to develop generalized erythematous lesions or urticaria after they had copper-containing IUD placed [120–125]. A 42-year-old woman developed palmoplantar pustulosis 2 years after IUD placed, and the pustules spread to her legs and buttocks during her menstrual period [9]. Within 1 month after IUD removal, all the symptoms had resolved. Patch test with copper elicited intraepidermal pustules and fever in 30 h [9]. The dermatitis caused by IUD can be persistent or occur intermittently during the perimenstrual period [9, 120–125]. The latency of dermatitis ranges from 2 weeks to several years. Most of the cases are only sensitized to copper sulfate according to the results of patch tests, while two cases showed positive patch results to both copper and nickel [120, 123].

Other Iatrogenic Invasive Routes

Besides implants, other iatrogenic invasive routes that may elicit SCD include intravenous injection, intramuscular injection, intraarticular injection, and intravesicular injection (Fig. 3). Most of the allergens reported are drugs, while only a few of them are metals. SCD caused via these routes often present as BS or SDRIFE.

Intravenous

During intravenous injection or infusion, allergens can enter the circulation rapidly. Therefore, a trace amount of allergen can elicit a severe SCD reaction. For example, nickel-sensitive patients react to 0.6–5.6 mg nickel in oral challenge tests, while 1–3 µg nickel intravenously is sufficient to induce severe SCD [4].

Drugs A few cases of SCD due to intravenous corticosteroids have been reported, manifesting as generalized eruption of eczema or maculopapular rash [126]. Ethylenediamine (EDA) in intravenous aminophylline was found to be the culprit of SCD presenting as Baboon syndrome [127–129].

Metals Theoretically, metals contained in cannulas can cause SCD in metal-allergic patients. Four nickel-sensitive patients suffered a generalized rash after intravenous therapy using cannulas which contained nickel-steel [130, 131]. A patient suffered generalized eczema after dialysis, and it was speculated that the cause was the nickel release from stainless-steel metal fitting in a dialysis system [132].

Intramuscular

Similar to intravenous corticosteroids, a few cases of SCD resulting from intramuscular corticosteroids have been reported [126]. In addition, an intramuscular injection of betamethasone sodium phosphate caused acute generalized exanthematous pustulosis in a patient who had been contact sensitized to betamethasone sodium phosphate previously [7]. In addition to corticosteroids, intramuscular injection of gold sodium thiomalate was reported to cause SCD in a patient whose patch test showed sensitization to gold [133].

Intraarticular

Similar to intravenous and intramuscular corticosteroids, a few cases of SCD due to intraarticular injection of corticosteroids have been reported [126]. Recently, Bianchi reported two cases of systemic allergic dermatitis from intraarticular triamcinolone acetonide [71].

Others

Intravesicular Diffused eczematous lesions are quite common after intravesical instillation of mitomycin C, since the allergen can get into the circulation through the bladder mucosa [134]. The dermatitis can be recognized as SCD if patch testing with the mitomycin C is positive [134].

Middle Ear The middle ear application of ampicillin solution was reported to cause baboon syndrome in a 63-year-old male [135].

Acupuncture Recently, our team reported a 70-year-old female diagnosed with SCD. She had a 2-month history of a generalized eczematous rash involving her arms, legs, and trunk. The dermatitis appeared after 1 week of acupuncture and worsened while she continued the acupuncture treatment. Laboratory tests showed that her absolute eosinophil count and her total IgE level were significantly elevated. Patch test showed positive reactions to cobalt chloride hexahydrate and potassium dichromate. Micro-X-ray fluorescence microspectroscopy was performed to confirm that the acupuncture needle as well as the artificial sweat immersed by the needle contained cobalt and chromium. After she stopped receiving acupuncture treatments, the rash resolved quickly, and her total IgE and eosinophil count returned to normal [15].

Conclusion

Systemic contact dermatitis is rare, and the treatment for SCD is limited and ineffective. Earlier identification of the culprit of SCD can avoid the worsening of symptoms and

lead to a better outcome. If doctors are not familiar with the presentations of SCD and the possible routes of allergen sensitization and exposure, the diagnosis of SCD may be delayed. We summarized all the routes through which allergens get into body and cause SCD, which will provide a comprehensive reference for the clinicians to identify the culprit of SCD and to optimize avoidance measures. The exact mechanisms behind SCD are not fully elucidated, and further investigations are needed.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12016-021-08873-2>.

Acknowledgements The figures are created with BioRender.com.

Funding This work was supported by the National Natural Science Foundation of China [grant number 81373175], the National Key Research and Development Program of China [grant number 2017YFA0403403], and CAMS Innovation Fund for Medical Sciences (No.2016-I2M-1003).

Declarations

Competing Interests The authors declare no competing interests.

References

1. Aquino M, Rosner G (2019) Systemic contact dermatitis. *Clin Rev Allergy Immunol* 56(1):9–18
2. Yoshihisa Y, Shimizu T (2012) Metal allergy and systemic contact dermatitis: an overview. *Dermatology Research and Practice* 2012:1–5
3. Fabbro SK, Zirwas MJ (2014) Systemic contact dermatitis to foods: nickel, BOP, and more. *Curr Allergy Asthma Rep* 14(10):463
4. Menné T et al (1994) Systemic contact dermatitis. *Am J Contact Dermatitis* 5(1):1–12
5. Suwarsa O et al (2017) Systemic contact dermatitis due to corrosion of titanium-coated nickel and cobalt bone plate fixation: A case report. *Medicine (Baltimore)* 96(50): p. e9120
6. Häusermann 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
7. Gambini D et al (2020) Systemic allergic dermatitis presenting as acute generalized exanthematous pustulosis due to betamethasone sodium phosphate. *Contact Dermatitis* 82(4):250–252
8. Yanagi T et al (2005) Zinc dental fillings and palmoplantar pustulosis. *Lancet* 366(9490):1050
9. Wen L, Xu T, Yin J (2008) Boils? Or coils? *Lancet* 372(9637):506
10. Corazza M et al (2019) Systemic allergic dermatitis due to gentamicin. *Contact Dermatitis* 81(5):402–403
11. Rundle CW, Machler BC, Jacob SE (2019) Pathogenesis and causations of systemic contact dermatitis. *G Ital Dermatol Venereol* 154(1):42–49
12. Jensen CS et al (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

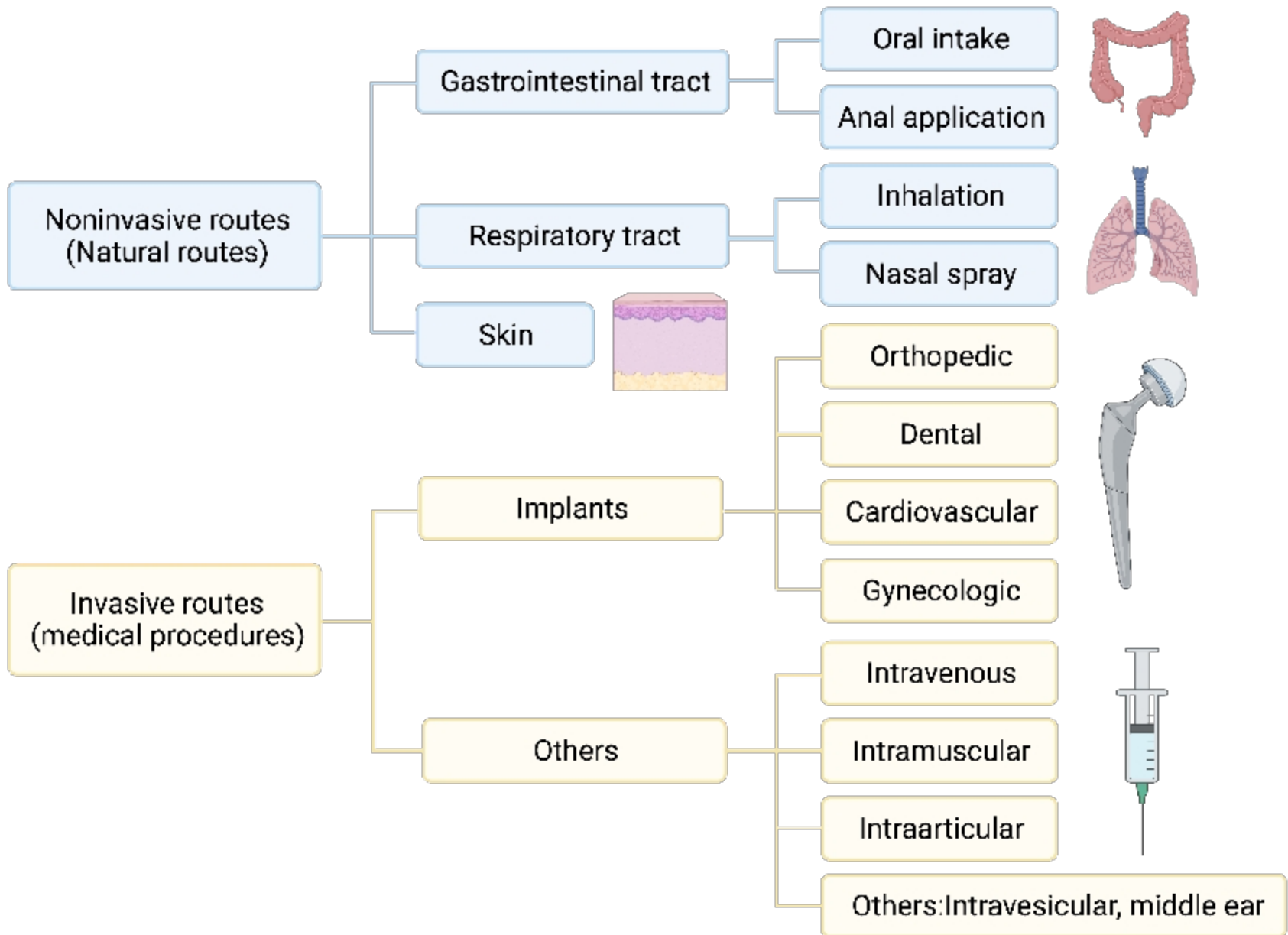
13. Wen L et al (2007) Baboon syndrome induced by mercury - first case report in China. *Contact Dermatitis* 56(6):356–357
14. Kunkeler L, Nieboer C, Bruynzeel DP (2000) Type III and type IV hypersensitivity reactions due to mitomycin C. *Contact Dermatitis* 42(2):74–76
15. Pan Z et al (2021) Systemic contact dermatitis caused by acupuncture: a neglected route of allergen entry. *Contact Dermatitis* 85(1):102–105
16. Matiz C, Jacob SE (2011) Systemic contact dermatitis in children: how an avoidance diet can make a difference. *Pediatr Dermatol* 28(4):368–374
17. Hayakawa R et al (1992) Systemic contact dermatitis due to aml-exanox. *Contact Dermatitis* 27(2):122–123
18. Pfützner W et al (2003) Systemic contact dermatitis elicited by oral intake of Balsam of Peru. *Acta Dermato Venereologica* 83(4):294–295
19. Salam TN, Fowler JF Jr (2001) Balsam-related systemic contact dermatitis. *J Am Acad Dermatol* 45(3):377–381
20. Burden AD et al (1994) Garlic-induced systemic contact dermatitis. *Contact Dermatitis* 30(5):299–300
21. Pereira F, Hatia M, Cardoso J (2002) Systemic contact dermatitis from diallyl disulfide. *Contact Dermatitis* 46(2):124–124
22. Cho E, Lee JD, Cho SH (2011) Systemic contact dermatitis from propolis ingestion. *Ann Dermatol* 23(1):85–88
23. Komericki P, Kränke B (2009) Maculopapular exanthem from propolis: case report and review of systemic cutaneous and non-cutaneous reactions. *Contact Dermatitis* 61(6):353–355
24. Rodríguez-Serna M et al (1998) Allergic and systemic contact dermatitis from *Matricaria chamomilla* tea. *Contact Dermatitis* 39(4):192–193
25. Rycroft RJ (2003) Recurrent facial dermatitis from chamomile tea. *Contact Dermatitis* 48(4):229
26. Cusack C, Buckley C (2005) Compositae dermatitis in a herbal medicine enthusiast. *Contact Dermatitis* 53(2):120–121
27. Wintzen M, Donker AS, van Zuuren EJ (2003) Recalcitrant atopic dermatitis due to allergy to Compositae. *Contact Dermatitis* 48(2):87–88
28. Lundh K et al (2006) Contact allergy to herbal teas derived from Asteraceae plants. *Contact Dermatitis* 54(4):196–201
29. Park SJ et al (2020) Systemic contact dermatitis induced by Rhus allergens in Korea: exercising caution in the consumption of this nutritious food. *Clin Exp Dermatol*
30. Yoo KH et al (2010) Ingestion of Rhus chicken causing systemic contact dermatitis in a Korean patient. *Clin Exp Dermatol* 35(7):756–758
31. Oh SH, Haw CR, Lee MH (2003) Clinical and immunologic features of systemic contact dermatitis from ingestion of Rhus (*Toxicodendron*). *Contact Dermatitis* 48(5):251–254
32. Cardinali C et al (2004) Systemic contact dermatitis from herbal and homeopathic preparations used for herpes virus treatment. *Acta Derm Venereol* 84(3):223–226
33. Park SD et al (2000) Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of Rhus (lacquer). *Br J Dermatol* 142(5):937–942
34. Fukushima S, Kidou M, Ihn H (2008) Fixed food eruption caused by cashew nut. *Allergol Int* 57(3):285–287
35. Marks JG Jr et al (1984) Dermatitis from cashew nuts. *J Am Acad Dermatol* 10(4):627–631
36. Thoo CH, Freeman S (2008) Hypersensitivity reaction to the ingestion of mango flesh. *Australas J Dermatol* 49(2):116–119
37. Kopp T et al (2009) Systemic allergic contact dermatitis due to consumption of raw shiitake mushroom. *Clinical & Experimental Dermatology* 34(8):e910–e913
38. Scheman A et al (2012) Food avoidance diets for systemic, lip, and oral contact allergy: an american contact alternatives group article. *Dermatitis* 23(6):248–257
39. Hill AM, Belsito DV (2003) Systemic contact dermatitis of the eyelids caused by formaldehyde derived from aspartame? *Contact Dermatitis* 49(5):258–259
40. Jacob SE, Zapolanski T (2008) Systemic contact dermatitis. *Dermatitis* 19(1):9–15
41. Lowther A, McCormick T, Nedorost S (2008) Systemic contact dermatitis from propylene glycol. *Dermatitis* 19(2):105–108
42. Dejobert Y et al (2001) Vesicular eczema and systemic contact dermatitis from sorbic acid. *Contact Dermatitis* 45(5):291
43. Giordano-Labadie F, Pech-Ormieres C, Bazex J (1996) Systemic contact dermatitis from sorbic acid. *Contact Dermatitis* 34(1):61–62
44. Roed-Petersen J, Hjorth N (1976) Contact dermatitis from anti-oxidants. *Br J Dermatol* 94(3):233–241
45. Meyer MD, Watsky KL (2015) Systemic contact dermatitis due to flaxseed ingestion. *Dermatitis* 26(5):241
46. Panaszek B et al (2017) Systemic contact dermatitis caused by cobalt chloride and palladium in a 26-year-old woman with allergic type I reactions, non-steroidal anti-inflammatory drug hypersensitivity and autoimmune thyroiditis. *Adv Dermatol Allergol* 4:388–390
47. Krecisz B et al (2011) Systemic contact dermatitis to nickel present in cocoa in 14-year-old boy. *Pediatr Dermatol* 28(3):335–336
48. Stuckert J, Nedorost S (2008) Low-cobalt diet for dyshidrotic eczema patients. *Contact Dermatitis* 59(6):361–365
49. Sakai T, Hatano Y, Fujiwara S (2013) Systemic contact dermatitis due to zinc successfully treated with a zinc-restricted diet: a case report. *Allergol Int* 62(2):265–267
50. Adachi A, Horikawa T (2007) Pompholyx of the infant possibly induced by systemic metal allergy to chromium in mother's milk. *Arerugi* 56(7):703–708
51. Vickers HR, Bagratuni L, Alexander S (1958) Dermatitis caused by penicillin in milk. *Lancet* 1(7016):351–352
52. Veien NK (2011) Systemic contact dermatitis. *Int J Dermatol* 50(12):1445–1456
53. Nijhawan RI et al (2009) Systemic contact dermatitis. *Dermatol Clin* 27(3): p. 355–64, vii
54. Miyahara A et al (2011) A new proposal for a clinical-oriented subclassification of baboon syndrome and a review of baboon syndrome. *Asian Pac J Allergy Immunol* 29(2):150–160
55. Thyssen JP, Menné T (2010) Metal allergy—a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem Res Toxicol* 23(2):309–318
56. 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): p. e58
57. Lerch M, Bircher AJ (2004) Systemically induced allergic exanthem from mercury. *Contact Dermatitis* 50(6):349–353
58. van Ulsen J, Stolz E, van Joost T (1988) Chromate dermatitis from a homeopathic drug. *Contact Dermatitis* 18(1):56–57
59. Fowler J (2000) Systemic contact dermatitis caused by oral chromium picolinate 65(2):116
60. Ozkaya E, Topkarci Z, Ozarmagan G (2010) Systemic allergic dermatitis from chromium in a multivitamin/multimineral tablet. *Contact Dermatitis* 62(3):184
61. De Marchi S, Cecchin E, De Marchi SU (2014) Systemic allergic dermatitis resulting from oral administration of chromium with a food supplement. *Contact Dermatitis* 70(2):123–125
62. Pongcharoensuk T, Thaiwat S (2021) Systemic pigmented contact dermatitis to cobalt following ingestion of cobalamin supplement. *Clin Case Rep* 9(5): p. e04103
63. Boonk WJ, van Ketel WG (1979) Nickel dermatitis after swallowing a nickel coin (Dutch florin). *Contact Dermatitis* 5(5):341–342

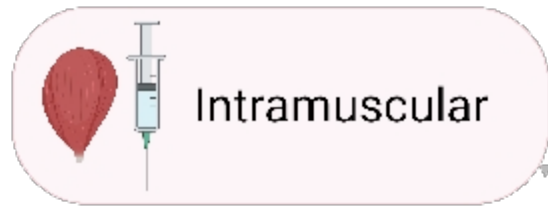
64. Mahdi G, Israel DM, Hassall E (1996) Nickel dermatitis and associated gastritis after coin ingestion. *J Pediatr Gastroenterol Nutr* 23(1):74–76
65. Tan MG et al (2020) Baboon syndrome from mercury showing leukocytoclastic vasculitis on biopsy. *Contact Dermatitis*
66. Saito N et al (2010) Generalized exacerbation of systemic allergic dermatitis due to zinc patch test and dental treatments. *Contact Dermatitis* 62(6):372–373
67. Barbaud A et al (2001) Sensitization to resorcinol in a prescription verrucide preparation: unusual systemic clinical features and prevalence. *Ann Dermatol Venereol* 128(5):615–618
68. Mussani F, Poon D, Skotnicki-Grant S (2013) Systemic contact dermatitis to topical clioquinol/hydrocortisone combination cream. *Dermatitis* 24(4):196–197
69. Nakada T, Matsuzawa Y (2012) Allergic contact dermatitis syndrome from buprenorphine for nursing infant. *Dermatitis* 23(4):185–186
70. Fernandez Redondo V et al (1994) Systemic contact dermatitis from erythromycin. *Contact Dermatitis* 30(5):311
71. Bianchi L et al (2016) Deflazacort hypersensitivity: a difficult-to-manage case of systemic allergic dermatitis and literature review. *Contact Dermatitis* 75(1):54–56
72. Zhang H, Xie Z (2021) Symmetrical drug-related intertriginous and flexural exanthema induced by metronidazole suppository. *Contact Dermatitis* 84(6):486–488
73. Shelley WB (1964) Chromium in welding fumes as cause of eczematous hand eruption. *JAMA* 189:772–773
74. Zuger C (1982) Chromium in welding fumes. *Contact Dermatitis* 8(1):69–70
75. Asano Y et al (2009) Occupational cobalt induced systemic contact dermatitis. *Eur J Dermatol* 19(2):166–167
76. Le Coz CJ et al (1996) An unusual case of mercurial baboon syndrome. *Contact Dermatitis* 35(2):112
77. Mahajan VK, Sharma NL, Sharma RC (2004) Parthenium dermatitis: is it a systemic contact dermatitis or an airborne contact dermatitis? *Contact Dermatitis* 51(5–6):231–234
78. Voltolini S, Fumagalli F (2020) Delayed corticosteroid hypersensitivity: a clinical management proposal. *Eur Ann Allergy Clin Immunol*
79. Al-Shaikhly T et al (2020) Systemic contact dermatitis to inhaled and intranasal corticosteroids. *Ann Allergy Asthma Immunol* 125(1):103–105
80. 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
81. Oliveira A et al (2011) Intertriginous and flexural exanthema after application of a topical anesthetic cream: a case of baboon syndrome. *Dermatitis* 22(6):360–362
82. Erdmann SM, Sachs B, Merk HF (2001) Systemic contact dermatitis from cinchocaine. *Contact Dermatitis* 44(4):260–261
83. Marques C et al (1995) Allergic contact dermatitis and systemic contact dermatitis from cinchocaine. *Contact Dermatitis* 33(6):443
84. Matos-Pires E et al (2018) Baboon syndrome caused by anti-haemorrhoidal ointment. *Contact Dermatitis* 78(2):170–171
85. Caro-Gutiérrez D et al (2015) Systemic contact dermatitis due to amethocaine following digital rectal examination. *Dermatol Online J* 21(5)
86. Gallo R, Parodi A (2002) Baboon syndrome from 5-aminosalicylic acid. *Contact Dermatitis* 46(2):110
87. Proske S et al (2003) Severe allergic contact dermatitis with generalized spread due to buprenorphine presenting as the “baboon” syndrome. *Dtsch Med Wochenschr* 128(11):545–547
88. Tonetti DA et al (2018) Use of pipeline endovascular device in patients with nickel allergies. *World Neurosurg* 120:349–351
89. Niki Y et al (2005) Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. *Biomaterials* 26(9):1019–1026
90. Basko-Plluska JL, Thyssen JP, Schalock PC (2011) Cutaneous and systemic hypersensitivity reactions to metallic implants. *Dermatitis* 22(2):65–79
91. Cobb HK et al (2017) Systemic contact dermatitis to a surgical implant presenting as red decorative tattoo reaction. *JAAD Case Rep* 3(4):348–350
92. Thomas P et al (2006) Hypersensitivity to titanium osteosynthesis with impaired fracture healing, eczema, and T-cell hyperresponsiveness in vitro: case report and review of the literature. *Contact Dermatitis* 55(4):199–202
93. Haeblerle M, Wittner B (2009) Is gentamicin-loaded bone cement a risk for developing systemic allergic dermatitis? *Contact Dermatitis* 60(3):176–177
94. Kanerva L, Förström L (2001) Allergic nickel and chromate hand dermatitis induced by orthopaedic metal implant. *Contact Dermatitis* 44(2):103–104
95. Gao X et al (2011) Dermatitis associated with chromium following total knee arthroplasty. *J Arthroplasty* 26(4): p. 665 e13–6
96. Merle C et al (1992) Generalized eczema from vitallium osteosynthesis material. *Contact Dermatitis* 27(4):257–258
97. Wong CC, Nixon RL (2014) Systemic allergic dermatitis caused by cobalt and cobalt toxicity from a metal on a metal hip replacement. *Contact Dermatitis* 71(2):113–114
98. Bizzotto N et al (2015) Chromium-induced diffuse dermatitis with lymph node involvement resulting from Langerhans cell histiocytosis after metal-on-metal hip resurfacing. *Br J Dermatol* 172(6):1633–1636
99. Carboni GP et al (1994) Dermatitis associated with orthopaedic prostheses and internal fixations. *Contact Dermatitis* 31(3):197–198
100. Thomas P et al (2006) Osteosynthesis associated contact dermatitis with unusual perpetuation of hyperactivity in a nickel allergic patient. *Contact Dermatitis* 54(4):222–225
101. Rostoker G et al (1987) Dermatitis due to orthopaedic implants. A review of the literature and report of three cases. *J Bone Joint Surg Am* 69(9): p. 1408–12
102. Veien NK et al (1994) Stomatitis or systemically-induced contact dermatitis from metal wire in orthodontic materials. *Contact Dermatitis* 30(4):210–213
103. Pigatto PD, Guzzi G (2004) Systemic contact dermatitis from nickel associated with orthodontic appliances. *Contact Dermatitis* 50(2):100–101
104. Mancuso G, Berdondini RM (2002) Eyelid dermatitis and conjunctivitis as sole manifestations of allergy to nickel in an orthodontic appliance. *Contact Dermatitis* 46(4):245
105. Kerosuo H, Kanerva L (1997) Systemic contact dermatitis caused by nickel in a stainless steel orthodontic appliance. *Contact Dermatitis* 36(2):112–113
106. Guimaraens D, Gonzalez M, Condé-Salazar L (1994) Systemic contact dermatitis from dental crowns. *Contact Dermatitis* 30(2):124–125
107. Hubler WJ, Hubler WS (1983) Dermatitis from a chromium dental plate. *Contact Dermatitis* 9(5):377–383
108. Ling DH et al (2018) Systemic contact dermatitis caused by cobalt-chromium-molybdenum alloy denture frameworks: a case report. *Zhonghua Kou Qiang Yi Xue Za Zhi* 53(7):486–487
109. Shimizu T, Kobayashi S, Tanaka M (2003) Systemic contact dermatitis to zinc in dental fillings. *Clin Exp Dermatol* 28(6):675–676
110. Pigatto PD, Zerboni R, Guzzi G (2008) Local and systemic allergic contact dermatitis due to dental alloys. *J Eur Acad Dermatol Venereol* 22(1):124–126
111. Hosoki M et al (2016) Allergic contact dermatitis caused by titanium screws and dental implants. *J Prosthodont Res* 60(3):213–219

112. Egusa H et al (2008) Suspected association of an allergic reaction with titanium dental implants: a clinical report. *J Prosthet Dent* 100(5):344–347
113. Honari G et al (2008) Hypersensitivity reactions associated with endovascular devices. *Contact Dermatitis* 59(1):7–22
114. Landwehr AJ, van Ketel WG (1983) Pompholyx after implantation of a nickel-containing pacemaker in a nickel-allergic patient. *Contact Dermatitis* 9(2):147
115. Raque C, Goldschmidt H (1970) Dermatitis associated with an implanted cardiac pacemaker. *Arch Dermatol* 102(6):646–649
116. Romaguera C, Grimalt F (1981) Pacemaker dermatitis. *Contact Dermatitis* 7(6):333
117. Giménez-Arnau A et al (2000) Metal-induced generalized pruriginous dermatitis and endovascular surgery. *Contact Dermatitis* 43(1):35–40
118. Joshi SR, Khan DA (2018) Effective use of dupilumab in managing systemic allergic contact dermatitis. *Dermatitis* 29(5):282–284
119. Jetty P et al (2013) Superficial femoral artery nitinol stent in a patient with nickel allergy. *J Vasc Surg* 58(5):1388–1390
120. Pujol RM et al (1998) Perimenstrual dermatitis secondary to a copper-containing intrauterine contraceptive device. *Contact Dermatitis* 38(5):288
121. Purello D'Ambrosio F et al (1996) Systemic contact dermatitis to copper-containing IUD. *Allergy* 51(9):658–659
122. Rongioletti F, Rivara G, Rebora A (1985) Contact dermatitis to a copper-containing intra-uterine device. *Contact Dermatitis* 13(5):343
123. Romaguera C, Grimalt F (1981) Contact dermatitis from a copper-containing intrauterine contraceptive device. *Contact Dermatitis* 7(3):163–164
124. Barranco VP (1972) Eczematous dermatitis caused by internal exposure to copper. *Arch Dermatol* 106(3):386–387
125. Gara S et al (2020) Systemic allergic dermatitis caused by a copper-containing intra-uterine device. *Contact Dermatitis*
126. Baeck M, Goossens A (2012) Systemic contact dermatitis to corticosteroids. *Allergy* 67(12):1580–1585
127. Guin JD, Fields P, Thomas KL (1999) Baboon syndrome from i.v. aminophylline in a patient allergic to ethylenediamine. *Contact Dermatitis* 40(3): p. 170–1
128. 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
129. Terzian CG, Simon PA (1992) Aminophylline hypersensitivity apparently due to ethylenediamine. *Ann Emerg Med* 21(3):312–314
130. Stoddart CJ (1960) Nickel sensitivity as a cause of infusion reactions. *Lancet* 276(7153): p. 741–742
131. Raison-Peyron N et al (2005) Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter. *Contact Dermatitis* 53(4):222–225
132. Olerud JE et al (1984) Presumptive nickel dermatitis from hemodialysis. *Arch Dermatol* 120(8):1066–1068
133. Möller H et al (1996) Flare-up at contact allergy sites in a gold-treated rheumatic patient. *Acta Derm Venereol* 76(1):55–58
134. Peitsch WK et al (2007) Hematogenous contact dermatitis after intravesicular instillation of mitomycin C. *Hautarzt* 58(3):246–249
135. Andersen KE, Hjorth N, Menné T (1984) The baboon syndrome: systemically-induced allergic contact dermatitis. *Contact Dermatitis* 10(2):97–100
136. Kosilek RP et al (2013) Automatic face classification of Cushing's syndrome in women - a novel screening approach. *Exp Clin Endocrinol Diabetes* 121(9):561–564
137. de Groot AC, Conemans J (1986) Allergic urticarial rash from oral codeine. *Contact Dermatitis* 14(4):209–214
138. Tagami H et al (1983) Delayed hypersensitivity in ampicillin-induced toxic epidermal necrolysis. *Arch Dermatol* 119(11):910–913
139. Wolf R, Elman M, Brenner S (1993) Drug-induced "intertrigo." *Int J Dermatol* 32(7):515–516
140. Goossens C, Sass U, Song M (1997) Baboon syndrome. *Dermatology* 194(4):421–422
141. Messegue J et al (1993) Systemic contact dermatitis from isoniazid. *Contact Dermatitis* 28(2):110–111
142. Fernandez L et al (1996) Systemic contact dermatitis from miconazole. *Contact Dermatitis* 34(3):217
143. Cooper SM, Reed J, Shaw S (1999) Systemic reaction to nystatin. *Contact Dermatitis* 41(6):345–346
144. Carnicle JM, Tran TV, McKissack SS (2021) Systemic contact dermatitis following oral neomycin therapy. *Proc (Bayl Univ Med Cent)* 34(1):89–90
145. Amichai B, Grunwald MH (2002) Baboon syndrome following oral roxithromycin. *Clin Exp Dermatol* 27(6):523
146. Weiss JM et al (2001) Reproducible drug exanthema to terbinafine with characteristic distribution of baboon syndrome. *Hautarzt* 52(12):1104–1106
147. 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
148. Treudler R, Simon JC (2006) Symmetric, drug-related, intertriginous, and flexural exanthema in a patient with polyvalent intolerance to corticosteroids. *J Allergy Clin Immunol* 118(4):965–967
149. Garcia-Bravo B, Repiso JB, Camacho F (2000) Systemic contact dermatitis due to deflazacort. *Contact Dermatitis* 43(6):359–360
150. Hindson C (1977) Contact eczema from methyl salicylate reproduced by oral aspirin (acetyl salicylic acid). *Contact Dermatitis* 3(6):348–349
151. Lakshmi C, Srinivas CR (2011) Systemic (allergic) contact dermatitis to diclofenac. *Indian J Dermatol Venereol Leprol* 77(4):536
152. Sans V et al (2008) Baboon syndrome induced by cetuximab. *Arch Dermatol* 144(2):272–274
153. Barbaud A et al (1999) A baboon syndrome induced by intravenous human immunoglobulins: report of a case and immunological analysis. *Dermatology* 199(3):258–260
154. Nadal C et al (1996) Systemic contact dermatitis from 5-fluorouracil. *Contact Dermatitis* 35(2):124–125
155. Akay BN, Sanli H (2009) Symmetrical drug-related intertriginous and flexural exanthema due to oral risperidone. *Pediatr Dermatol* 26(2):214–216
156. Pigatto PD et al (1987) Phenobarbital-induced allergic dermatitis. *Contact Dermatitis* 16(5):279
157. Watanabe T et al (2010) A case of symmetrical drug-related intertriginous and flexural exanthema induced by loflazepate ethyl. *J Eur Acad Dermatol Venereol* 24(3):357–358
158. Machel L et al (1992) Patch testing with clobazam: relapse of generalized drug eruption. *Contact Dermatitis* 26(5):347–348
159. Chowdhury MM et al (1999) Hydroxyurea-induced skin disease mimicking the baboon syndrome. *Clin Exp Dermatol* 24(4):336–337
160. Helmbold P et al (1998) Symmetric psychotropic and nonpigmenting fixed drug eruption due to cimetidine (so-called baboon syndrome). *Dermatology* 197(4):402–403
161. Ravenscroft J, Goulden V, Wilkinson M (2001) Systemic allergic contact dermatitis to 8-methoxypsoralen (8-MOP). *J Am Acad Dermatol* 45(6 Suppl):S218–S219
162. Sánchez TS et al (2000) Flare-up reaction of pseudoephedrine baboon syndrome after positive patch test. *Contact Dermatitis* 42(5):312–313
163. Sánchez-Morillas L et al (2003) Baboon syndrome due to pseudoephedrine. *Contact Dermatitis* 48(4):234
164. Gutgesell C, Fuchs T (2001) Orally elicited allergic contact dermatitis to tetraethylthiuramdisulfide. *Am J Contact Dermat* 12(4):235–236

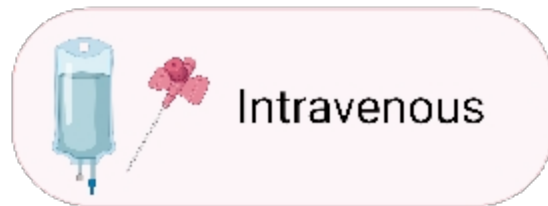
165. Daito J et al (2009) Symmetrical drug-related intertriginous and flexural exanthema caused by valacyclovir. *Dermatology* 218(1):60–62
166. Bajaj AK et al (2001) Occupational and systemic contact dermatitis with photosensitivity due to vitamin B6. *Contact Dermatitis* 44(3):184
167. Arnold AW et al (2007) Recurrent flexural exanthema (SDRIFE or baboon syndrome) after administration of two different iodinated radio contrast media. *Dermatology* 214(1):89–93
168. Gonçalo M et al (1999) Allergic and systemic contact dermatitis from estradiol. *Contact Dermatitis* 40(1):58–59

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Intramuscular



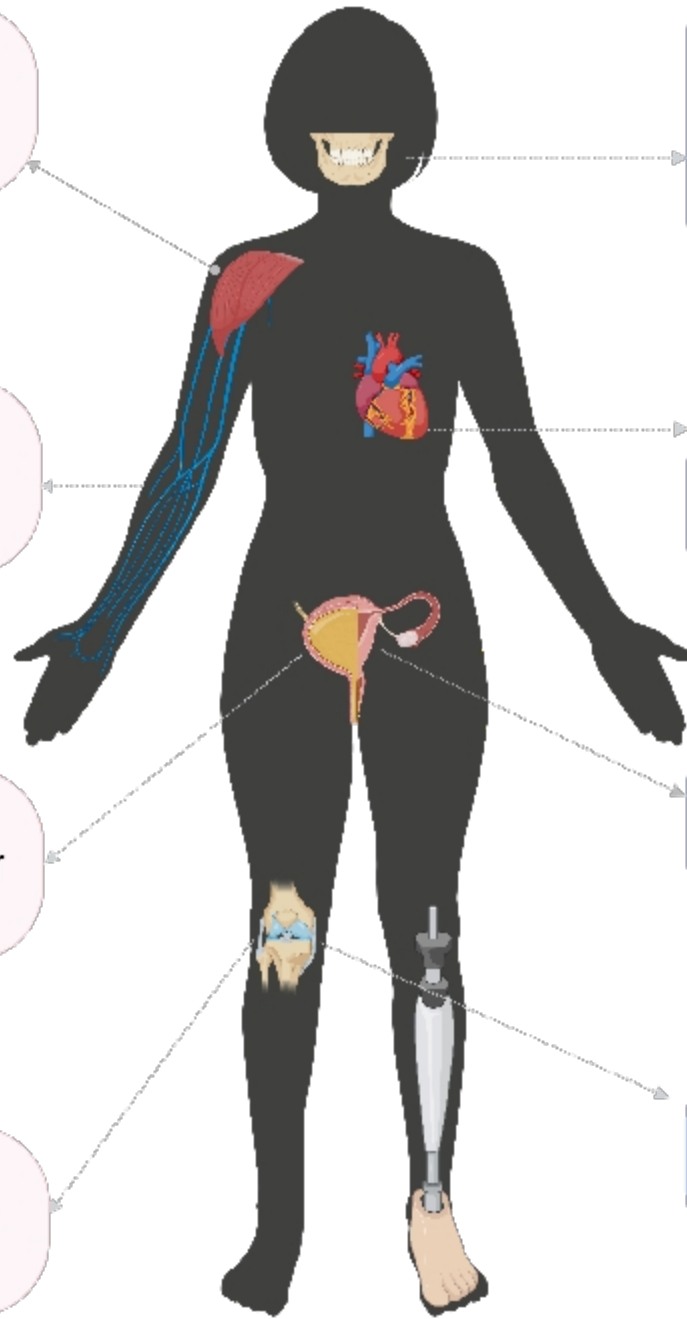
Intravenous



Intravesicular



Intraarticular



Dental

- dental fillings
- dentures
- dental plate
- dental crowns
- orthodontic materials



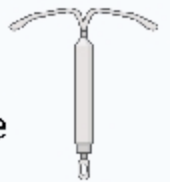
Cardiovascular

- pacemaker
- endovascular prosthesis



Gynecologic

- intrauterine device



Orthopedic

- dynamic joint prosthesis
- static prosthesis

