POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics

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Nickel Allergic Contact Dermatitis: Identification, Treatment, and Prevention

Nanette B. Silverberg, MD, FAAP, FAAD,[a] Janice L. Pelletier, MD, FAAP,[b,c] Sharon E. Jacob, MD, FAAP, FAAD,[d,e] Lynda C. Schneider, MD, FAAP,[f] SECTION ON DERMATOLOGY, SECTION ON ALLERGY AND IMMUNOLOGY

Nickel is a ubiquitous metal added to jewelry and metallic substances for its hardening properties and because it is inexpensive. Estimates suggest that at least 1.1 million children in the United States are sensitized to nickel. Nickel allergic contact dermatitis (Ni-ACD) is the most common cutaneous delayed-type hypersensitivity reaction worldwide. The incidence among children tested has almost quadrupled over the past 3 decades. The associated morbidities include itch, discomfort, school absence, and reduced quality of life. In adulthood, individuals with Ni-ACD may have severe disabling hand eczema. The increasing rate of Ni-ACD in children has been postulated to result from early and frequent exposure to metals with high amounts of nickel release (eg, as occurs with ear piercing or with products used daily in childhood such as toys, belt buckles, and electronics).

To reduce exposure to metal sources with high nickel release by prolonged and direct contact with human skin, Denmark and the European Union legislated a directive several decades ago with the goal of reducing high nickel release and the incidence of Ni-ACD. Since then, there has been a global reduction in incidence of Ni-ACD in population-based studies of adults and studies of children and young adults being tested for allergic contact dermatitis. These data point to nickel exposure as a trigger for elicitation of Ni-ACD and, further, provide evidence that legislation can have a favorable effect on the economic and medical health of a population.

This policy statement reviews the epidemiology, history, and appearances of Ni-ACD. Examples of sources of high nickel release are discussed to highlight how difficult it is to avoid this metal in modern daily lives. Treatments are outlined, and avoidance strategies are presented. Long-term epidemiological interventions are addressed. Advocacy for smarter nickel use is reviewed. The American Academy of Pediatrics supports US legislation that advances safety standards (as modeled by the European Union) that protect children from early and prolonged skin exposure to high–nickel-releasing items. Our final aim for this article is to aid the pediatric community in developing nickel-avoidance strategies on both individual and global levels.

abstract

[a]Departments of Dermatology and Pediatrics, Mt Sinai Hospital and Icahn School of Medicine at Mt Sinai, New York, New York; [b]Northern Light Health, Bangor, Maine; [c]College of Medicine, University of New England, Biddeford, Maine; [d]Department of Dermatology, Loma Linda University, Loma Linda, California; [e]Departments of Medicine and Pediatrics, University of California, Riverside, California; and [f]Department of Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts

Drs Silverberg, Pelletier, Jacob, and Schneider fully participated in the conceptualization, drafting, and revision of this manuscript, and all authors approved the final manuscript as submitted.

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INTRODUCTION

Nickel Is a Common Cutaneous Allergen

Recent estimates suggest that 1.1 million children in the United States are potentially sensitized to nickel[1]; however, this may be a gross underestimate given that nickel allergic contact dermatitis (Ni-ACD) is found in approximately one-quarter of children who undergo patch testing. Nickel is present in metallic items that are common in children's environments, including earrings, watches, toys, and fasteners on clothing and belts. Chronic exposure to nickel increases risk for Ni-ACD. Nickel has become the most common metallic cause of allergic dermatitis and was named the "Contact Allergen of the Year" in 2008 by the American Contact Dermatitis Society. Determining the presence of Ni-ACD in those with allergic dermatitis can be difficult and elusive, with patch testing being a crucial tool used to help differentiate Ni-ACD from other forms of dermatitis.[2] The risk of Ni-ACD increases when ears are pierced.[3]

Nickel Exposures Are Common

Nickel is a ubiquitous metal, being the fifth most common element in the world. Worldwide use of nickel in the production of hardened metal items has been increasing since World War II.[4] The process by which nickel use shifted from coins and military purposes to daily use products, such as clothes and electronics, was strongly influenced by metal use in the post–World War II era. Among adults who were screened in Massachusetts General Hospital from 1996 to 2006, Ni-ACD was found in 22.1% of those 20 to 40 years of age but in only 10.1% of those older than 60 years, suggesting that Ni-ACD is a problem of younger individuals (those raised or those who had their ears pierced after World War II).[5] Today, nickel has continued to be a leading production metal in home and personal goods. Over time, Ni-ACD evolved from an occupational eczema of electroplaters to a common form of allergic contact dermatitis (ACD) among both adults and children, currently affecting as many as 20% of Americans. Historically, Ni-ACD has been linked to a wide range of exposures, including suspenders in the 1950s–1960s; zippers, buttons, and rivets in the 1970s; and ear piercing in the 1980s.[4] Environmental nickel present in oxides and sulfides is not as allergenic as the free nickel present in metal fittings found in industry.[4,6]

Nickel Allergy Has Significant Symptomatology

Virtually any site of the body can be affected by Ni-ACD, but some of the more commonly affected areas are the eyelids (transfer from hands), face, neck, wrists, fingers and hands, periumbilical area, and thighs.[7] Symptoms and signs of Ni-ACD range from mild dermatitis with pruritus, to deep erythema with oozing and papulation, to a systemic reaction with generalized idiopathic hypersensitivity.[6,7] Although Ni-ACD is a delayed-type hypersensitivity, symptoms can occur within the first 30 minutes of exposure through a complex cascade of inflammatory mediators generated after sensitization.[8]

KEY POINTS IN THE EVOLUTION OF NICKEL ALLERGY AS A SERIOUS ALLERGEN

Introduction of Nickel Into the Manufacturing of Metals

Nickel was first identified as an element in 1751 by a Swiss chemist named Axel Cronstedt. In the 1800s, nickel was introduced into the manufacturing of metal alloys with copper and zinc. As an alloy, its high value is related to many inherent qualities: high strength, lengthy life, anticorrosion, heat resistance, low cost, and minimal maintenance. In the mid-1800s, coins in the United States were alloyed with copper. In the late 1800s, steel production accelerated because of the strength of steel products. During the 20th century, nickel gained a solid place in industry as part of manufactured stainless steel alloy (along with chromate and iron). Today, two-thirds of nickel production in the world is devoted to the manufacture of stainless steel, 20% is for other specialized steel alloys (for military and aerospace), 9% is for plating, and the remainder is for various uses, including batteries, coins, and electronics.[9,10]

Early Reporting of Nickel Allergy

Weston et al[11] first reported Ni-ACD in young pediatric patients in 1984. Until that point, it was unclear whether cutaneous immune function in infants was mature enough to mount such responses. After the report of this phenomenon by Weston et al,[11] more attention to allergic reactions in infants and young children made it clear that contact allergy to nickel can begin in infancy, with some authors indicating increasing incidence after the age of 5 years.[12–16] Nickel's place as a cause of contact dermatitis in pediatrics was solidified by these early reports.

Ni-ACD can cause systemic hypersensitivity in children, and this was elucidated in 2 articles in 2002. Silverberg et al[16] reported a group of 30 children with clinical features of Ni-ACD manifested by persistent umbilical or wrist dermatitis. In that cohort, all children had positive results on patch testing for nickel; furthermore, 50% had an idiopathic hypersensitivity reaction, a hypersensitivity response characterized by the presence of inflammatory papules on the extensor surfaces of the extremities in sites not exposed to nickel.[17] A similar article from Sharma et al[17] reviewed 38 children with periumbilical papules consistent with Ni-ACD, all of whom demonstrated an idiopathic reaction.[18] Systemic contact

dermatitis has been defined as "a generalized ACD rash from systemic administration of a drug, chemical, or food to which the patient previously experienced ACD." There is no known general population-based prevalence of systemic nickel hypersensitivity, neither for kids nor for adults. Strongly positive (≥3 papular) nickel patch test results in these patients suggest that severe reactions correlate with systemic disease.[17]

Pathophysiology and Genetics of Nickel Allergic Sensitization

Nickel-contact allergy is a delayed-type (type IV) cutaneous hypersensitivity reaction that develops through a biphasic process: an induction phase is followed by an elicitation phase. In the induction phase, there are repeat exposures to free nickel that are beyond a minimal threshold. During this initial phase, an antigen is presented by the skin's dendritic cells to T cells (T helper 1 and T helper 17 cells), which causes the skin to develop a set of memory T cells that specifically recognize nickel. During the elicitation phase, there is amplification of the allergy through subsequent repetitive exposures that result in the manifestations of ACD.[4,6,18]

Ni-ACD is influenced by a combination of genetic and environmental factors, the latter being more important, according to leading experts.[4] Filaggrin mutations are associated with increased Ni-ACD risk. Another genetic determinant that may increase risk for Ni-ACD is HLA antigen expression.[19,20] Staphylococcal biofilms may promote the development of Ni-ACD in the setting of atopic dermatitis.[21]

Menné and Holm[22] showed a twin concordance rate of 29% in patients with Ni-ACD, confirmed from a population-based survey. Half of the pediatric patients with severe Ni-ACD with additional idiopathic reactions had a parent with Ni-ACD in the Silverberg et al[16] cohort, a statistic that is higher than that in the general population.

Product Properties That Contribute to Allergenicity

The amount of nickel released to the skin from contact with a metal object (not the presence of nickel) determines the potential for causing Ni-ACD. The development of Ni-ACD from contact with a nickel-containing object is promoted in a 3-step process: "1) the nickel in the material must be corroded, 2) the resulting nickel compounds must be solubilized, and 3) the nickel ions must be absorbed by the skin to cause a reaction."[23,24] Other contributory factors include the use of products under occlusion (eg, piercing holes) or prolonged contact with the skin such that sweat may erode or release nickel (eg, underside of the thighs against a chair).

Rising Prevalence of Nickel Allergy

The prevalence of nickel allergy in North America has increased significantly since the 1980s in both adults and children. Data on prevalence in the United States are derived from patch testing, that is, epicutaneous allergy testing, which reveals contact sensitization but not relevance of the allergy, outcomes, and/or associated disabilities. The North American Contact Dermatitis Group (NACDG) reported that nickel sensitization rates increased steadily between 1970 and 2002 in a mixed group of adults and children from 11% to 16.9%.[25] Pediatric-specific data from Peltonen[26] revealed a prevalence of Ni-ACD of 2.5% in 1981, and the NACDG series from 2001 to 2004 demonstrated 28.3% of children with positive patch test results were nickel allergic, showing an increase even more substantial in childhood than in adulthood.[27] One series revealed that although not all children with Ni-ACD have disabling symptoms, for those who undergo a patch test series, Ni-ACD represents a common relevant allergen, being detected in as many as 36.8% of children and adolescents tested and having an 80.4% relevance (ie, being identified as contributing to dermatitis activity).[28]

Population-based screening on individuals (including adults) referred for patch testing have highlighted the pervasive issue of Ni-ACD in the United States. In 1978, a population-based study of 1158 people identified 9% of individuals with Ni-ACD,[1] and approximately 50% of those who were nickel allergic had never sought medical care.[26] In a recent meta-analysis of 5 ACD studies representing 1507 pediatric subjects, 22.9% had Ni-ACD.[29] The current estimate of Ni-ACD in children with suspected ACD who are patch tested is 28.3% according to the NACDG.[27]

Data from Denmark are the most revealing when evaluating European Union (EU) nickel directives because Denmark introduced the directives in 1990, 14 years before widespread EU adoption. The Nickel Directive states that "consumer items intended to be in direct and prolonged contact with the skin were not allowed to release more than 0.5 mcg nickel/cm^2/week." This legislation was intended to reduce Ni-ACD but not eliminate disease. The venture has been successful in reducing Ni-ACD in young women with ear piercings who are patch tested. One particular outcome has been reduced severity of reaction on epicutaneous patch testing to nickel, which suggests less severity of disease. On the other hand, because the sale of nickel-laden agents is not criminalized, sales of items with nickel release persist in Europe, especially in outdoor flea markets.[3,30]

Before EU legislation, the percentage of female first-year college students in Finland in 1995 with Ni-ACD was 39%, suggesting that the rate may continue to increase further in the United States if no population-based

restrictions are enacted.[29,31,32] Population-based data on true nickel allergy in adolescents derived from survey data in Sweden reported in 2008, 7 years after EU legislation was put into action, revealed that 14.8% of 6095 adolescents polled believed they had Ni-ACD, with confirmation in 9.9%, revealing how EU nickel directives may be benefiting adolescents.[33] Data from a Danish pediatric contact dermatology database reveal ongoing reduction in nickel sensitization, with ACD rates of 9.7% in those tested (252 of 2587) from 2003 to 2011 and 7% (107 of 1540) from 2012 to 2016 (adjusted odds ratio, 0.69; 95% confidence interval, 0.55–0.88). Predominance of girls in the Ni-ACD group persisted in this study, as with previous studies.[33,34]

Piercings and Jewelry Are Leading Sources of Nickel Sensitization

Piercings, costume jewelry, watches, belt buckles, and clothing fasteners (grommets, buttons, studs, and toggles) are leading sources of epicutaneous nickel sensitization in countries without legislation controlling nickel release.[6] The same 1995 Finnish study of first-year college students revealed that piercings in female students were associated with a rate of 42% nickel allergy, compared withs 14% for female students without piercings.[31] A study of 960 girls 8 to 15 years of age in Sweden (published in 1985) with piercings revealed that 13% were nickel allergic, compared with 1% of girls without piercings.[23] In patch testing of school-aged girls for Ni-ACD from 1999 to 2000, older girls who had piercings before Danish regulations were implemented were 4 to 5 times as likely as those who had piercings after regulations to be allergic to nickel (17.1% vs 3.9%, respectively). A Norwegian pediatric contact allergy study of 7- to 12-year-old schoolchildren, published in 1994, identified a rate of 30.8% nickel allergy in children with piercings, compared with 16.3% in children without piercings.[35,36] Nickel allergy in girls with pierced ears has dramatically decreased in Denmark over the last 3 decades since strict nickel-release legislation was enacted.[14] Although piercings have been linked to nickel sensitization, occurrence of Ni-ACD is also common in children without piercings; therefore, reduction of nickel release is needed across all costume jewelry types.[6] A recent review of NACDG data revealed that of 1894 pediatric patients who were patch tested, 23.7% had nickel contact dermatitis and 36.4% had a pattern of skin disease consistent with all types of jewelry as the source of the nickel.[37]

The High Cost of Nickel Allergy in the United States

The 2004 estimates in the United States suggest that contact dermatitis, which includes nickel sensitization, accounted for $1.918 billion in health care costs (including direct medical costs and lost productivity costs) and affected 72.29 million people. Given that nickel-contact sensitization is noted in approximately one-quarter of patients, it is likely that nickel allergy contributes heavily to this burden.[24] Recent data from the American Academy of Dermatology reveal that contact allergy costs more than $1.5 billion in 2013.[38] Given that nickel allergy is the number one allergen nationwide in all age groups, nickel allergy is costly.

Other Sources of Nickel-Contact Sensitization

Contact with commonplace nickel alloy metallic products, such as toys, can lead to nickel release that deposits on a child's skin.[39,40] In a recent radiograph fluorescence spectroscopy study of US jewelry, 79 of 96 samples released nickel.[41] In a case series of children and adolescents from Brazil, the source of nickel exposure in the setting of Ni-ACD included jewelry piercings; metal clothing appliques on garments, accessories, and shoes; nail clippers; razor blades; and cosmetics.[1] Newer nickel sources reported to cause dermatitis include devices such as metallic cell phone cases (a persistent plaque on the hollow of the cheek), laptop cases and handheld device cases (fingertip, hand, lap, and periocular dermatitis), makeup applicators and ferrules (site of application), eye makeup, dog tag necklaces, and lip balm containers (lip and perioral).[42–48] Table 1 contains a brief compendium of items of daily use linked to nickel exposure and allergy.[4,6] Many of these newer nickel sources are more difficult to diagnose because the site of allergy can be areas not in direct contact, for example, the eyes.[43] The timing and type of nickel exposures throughout life are important. Ni-ACD was shown to be much less common when ear piercing occurred after placement of metal dental braces, compared with when piercing occurred before exposure to braces. So, less nickel sensitization may occur if placement of braces occurs first and piercing later.[44] This phenomenon may be analogous to the enteral tolerance that develops to lessen peanut allergy and may be akin to reasoning forwarded by the Learning Early About Peanut Allergy study.[49]

THE CLINICAL APPEARANCE OF NICKEL CONTACT DERMATITIS IS PROTEAN

Ni-ACD commonly is diagnosed on the basis of the appearance of itchy, persistent, erythematous, and/or lichenified papules and plaques that appear to conform to the area matching the exposure pattern of the metal object with the skin, for example, a circular erythematous plaque on the extensor wrist at the site of exposure to the backside of the wristwatch. Ni-ACD can also be caused by a child playing with a nickel-releasing object and then transferring the nickel to other sites.[1,45,46] Ni-ACD has also been described with nail polish from

TABLE 1 Sources of Nickel Exposure in Children

Sources
Artwork
White metal statues
Cleaners and detergents
Steel wool
Coins
Cooking
Pans
Pots
Stainless steel cookware used to cook acidic foods
Utensils (eg, silverware, spatula, and tongs)
Electronics
Batteries
Cell phone cases and electric shavers[a]
Mobile phones[a]
Laptops[a]
Tablets[a]
Foods (Mislankar and Zirwas[50] and Sharma[51])
Especially canned food
Seafood
Beans
Chocolate
Furniture
Brushed-metal furniture
Metal fittings and studs
Grooming
Nail clippers
Razors
Hair clips
Bobby pins
Metal brushes
Curling irons
Implants
Cardiac
Dental
Orthopedic
Keys
Makeup
Eyelash curlers
Ferrules
Lip balm containers
Musical instruments
Horns
Wind instrument mouthpieces
Occupational
Metal workers
Miners
Hospital cleaning staff
Ornamentation
Accessories
Ball and chain necklaces[a]
Belt buckles and/or belts[a]
Button flies[a]
Glasses
Grommets
Jewelry (costume, white gold, and low-karat gold)[a]
Earrings[a]
Necklaces[a]
Rings[a]
Watches[a]
Overalls
Rivets
Snaps
Zippers
Scissors
Tools
Toys

Adapted from Jacob SE, Goldenberg A, Pelletier JL, Fonacier LS, Usatine R, Silverberg N. Nickel allergy and our children's health: a review of indexed cases and a view of future prevention. *Pediatr Dermatol.* 2015;32(6):779–78 and Tuchman M, Silverberg JI, Jacob SE, Silverberg N. Nickel contact dermatitis in children. *Clin Dermatol.* 2015;33(3):320–326.

[a] The most commonly identified nickel-allergy sources in clinical practice.

a bottle with nickel metal balls included.[47] This itchy rash is often diffuse and can occur on other less common areas, such as the scalp and eyelids.

Other jewelry-related patterns of appearance include a plaque over the upper back at the site of a necklace clasp pressed against the skin, periumbilical plaques at the site of belt buckle or button fly skin contact, midback plaques where bra hooks press against the skin, and earring plaques and/or nodules at the site of piercing because of exposure to high–nickel-releasing earring posts.[16,17,48] Dental amalgams are rarely high nickel releasing, but they still can cause oral lesions such as persistent oral lichenoid reactions near the amalgam, anesthetic sensation, and/or systemic lesions.[52]

When the source of nickel shifts against the skin, (eg, chair nail heads, belt buckles, and coins in the pocket), the contact dermatitis may be more papular and/or diffuse, making the source less obvious. Furthermore, patients with atopic dermatitis may have background disease activity that prevents the margins of the Ni-ACD from being clearly distinguished.[4,16,17,53] In adults, nickel has been identified as a contact allergen that can worsen palmoplantar or scalp psoriasis.[54]

Idiopathic reactions, or diffuse hypersensitivity reactions, to nickel can occur. These may be associated with dietary or complementary supplements as the source of nickel ingestion,[55] creating generalized pruritus and exacerbating pruritus at the site of cutaneous nickel exposure, or they may come from a generalized idiopathic hypersensitivity reaction triggered by ongoing cutaneous exposures (a type of systemic contact dermatitis), the latter of which is manifested by extensor papules and lichenoid (flat-topped) papules and plaques over extensor surfaces. Idiopathic reactions (also called dermatophytid) are similar to those seen in some patients with tinea capitis when starting oral griseofulvin therapy.[4,6]

Dental amalgams, caps, and braces that contain or release nickel in higher concentration are associated with perioral Ni-ACD as well as Ni-ACD in eccentric sites such as ears, the waist, and wrists. Ni-ACD may precede or be caused by dental devices containing nickel. Furthermore, such Ni-ACD can be associated with lip swelling and a burning oral sensation.[52,56–58]

Although most allergic reactions to nickel are of a type IV delayed-type hypersensitivity, rare reports have appeared in the literature of individuals with systemic nickel hypersensitivity of a type I or immediate-type hypersensitivity. Other types of allergic reactions to nickel may occur after oral nickel exposure, causing symptoms as minor as flares of earlier nickel-allergic eczema sites, to a generalized maculopapular or vasculitislike rash, to more severe symptoms, including urticaria, headache malaise, diarrhea, fever, and arthralgia.[59,60] Skin prick testing has been performed in rare cases but remains controversial.[52,59,60] It is still most likely, even in such settings, that the reaction to nickel is a delayed-type hypersensitivity because rapid

reactions as fast as 10 to 30 minutes can be described in Ni-ACD delayed type.[61] The data on these cases are extremely limited, and no recommendation can be made until additional broad-based population data become available for testing.

OVERLAP WITH ATOPIC DERMATITIS

The NACDG demonstrated that 34% of children with a positive contact allergy result on testing had concurrent atopic dermatitis.[62] In children with atopic dermatitis, Ni-ACD can trigger severe exacerbations of pruritus.[6] In the setting of atopic dermatitis, Ni-ACD overlap is associated with more extensive atopic dermatitis and greater difficulty in diagnosing Ni-ACD.[7] Because the background population data on nickel allergy does not differ in prevalence, Ni-ACD can only be viewed as an aggravating or obscuring factor and not necessarily as a cause of disease.

MANAGEMENT OF NI-ACD

The broad goals of medical therapy in Ni-ACD are as follows:

1. identification and avoidance of nickel;
2. treatment of skin inflammation; and
3. restoration of the skin barrier and skin protection.

Identification and Avoidance of Nickel

Identifying sources of nickel requires investigation of personal adornments, hobbies (eg, instruments played), and jobs (eg, leisure-time activities and review of everyday device usage). Patients should be asked about garments or uniforms worn at work or school. Avoidance of nickel can be enhanced through testing objects for nickel content (see Avoidance of Nickel Exposure in Childhood section). Using Table 1 as a guide, pediatricians can ask patients targeted questions to determine nickel sources hidden in daily activities.

One of the hallmarks of good clinical care in ACD is education on how to avoid allergen-laden goods. Such is the case in Ni-ACD. Patients with Ni-ACD can be counseled to recognize objects that may be high-release nickel, to test such objects, and to protect the skin from prolonged and direct contact with the objects. Table 2 is a handout that can be used to help educate parents and children and adolescents about nickel avoidance. In general, piercing with nickel-free earrings can minimize risk of Ni-ACD, as can use of low-release nickel, but the latter still results in some release of nickel. Sterling silver (which is 92.5% pure silver), 18-karat yellow gold (which is 75% gold) or more-pure gold, platinum, titanium, and plastic earrings are alternatives that have low or no nickel content. Silver that is not sterling, such as nickel silver, 800 silver (80% silver), and German silver (which contains no silver at all; an alloy of nickel and zinc), are not ideal for the patient with Ni-ACD.

TABLE 2 Handout for Patients

Nickel is a metal that is added to many metal objects to harden them. Nickel can be found in almost all costume jewelry (including earrings, necklaces, watch backs, rings, and bracelets), some belt buckles, and such jewelry as ball and chain necklaces, dog tags, metal tabs, grommets, and button flies.

When you sweat, the nickel is released from the metal, even if it is only a small amount or percentage of the metal. Stainless steel is a stronger white metal and does not release nickel as easily.

If you are allergic to nickel, your rash will keep returning until you avoid nickel completely. There are many steps required to avoid nickel completely. It is not easy, but it is necessary to make you feel better.

1. Remove all nonessential metal from your clothing; replace button flies with plastic buttons and wear a belt that ties or has a plastic buckle.
2. For metal that you cannot remove, such as grommets on the side pockets of your jeans or the back of your watch, coat with 2 coats of clear nail polish every week or after washings.
3. Avoid sitting in shorts on metal chairs or plastic chairs with metal tabs.
4. Do not cook acidic foods in stainless steel cookware. Avoid stainless steel cookware if you can.
5. Tucking in your shirt does not prevent you from reacting to the nickel in your belt buckle or button fly.
6. Avoid ear piercing, especially if dental work, such as braces, is expected.
7. Sources of nickel in jewelry include costume jewelry, including earring posts that are not stainless steel, white gold, and all low-karat gold jewelry. Sterling silver and high-karat yellow gold jewelry are expected to have a low content of nickel but are not generally nickel free.
8. Tests to look for nickel released from household metals can be found at the following Web sites: https://nonickel.com/collections/nickel-test-kit-for-jewelry-and-meteorites and https://www.delasco.com/spot-test-for-nickel/. More information can be found at https://athenaallergy.com/pages/how-to-test-for-nickel-using-nickel-alert-dimethylglyoxime-test.

Treatment of Skin Inflammation

Inflammatory symptoms, including eczematous changes and pruritus, are the main symptoms of Ni-ACD–induced inflammation. There is no US Food and Drug Administration–approved therapy for Ni-ACD; however, Ni-ACD is a steroid-responsive dermatosis, and therefore topical corticosteroids may be helpful in conjunction with prevention of retriggering of dermatitis through avoidance of suspected sources of nickel exposure and with therapeutics to aid in pruritus or itch reduction. Although no specific regimen of topical corticosteroids has been endorsed by any organization for Ni-ACD, the American Academy of Pediatrics recommends choosing the corticosteroid class on the basis of the site of application and severity. Like in atopic dermatitis, off-label use of topical calcineurin inhibitors (eg, pimecrolimus and tacrolimus) can be effective in steroid-resistant Ni-ACD cases.[63,64] These topical therapies are used in combination with nickel avoidance, which is the cornerstone of treatment of Ni-ACD. Prevention is

paramount because there is no cure for Ni-ACD and because the disease is lifelong.[65] In recalcitrant cases or in the setting of severe Ni-ACD and severe pruritus or for those with widespread lesions, oral steroids for several days and then tapered, together with antihistamines for pruritus, can aid in symptomatic resolution.[66]

Restoration of the Skin Barrier and Skin Protection

Emollients can be used to enhance the skin barrier in children with atopic dermatitis and may benefit children with Ni-ACD and concurrent dermatitis symptoms. Skin protection can be achieved through thick physical blockage of nickel-containing metal objects, for example, cell phone cases, backing button flies in denim, or replacing metal buttons with plastic buttons. Thin fabrics and strategies such as tucking in one's shirt may not be fully protective.[4,53]

Confirmation of Suspected Ni-ACD

When a typical pattern of Ni-ACD appears on the wrist or periumbilical region, no confirmatory testing is needed.[16,17,67] In some cases in which suspicion is harder to confirm, patch testing, otherwise known as epicutaneous skin testing, is a form of testing in which a dilute version of the allergen is placed in a hypoallergenic well (sometimes called a Finn chamber) and applied to the back. Contact time with the skin of the upper back or inner upper arms is up to 48 hours. After this period, the patches are removed, and the test results are read. The patches are read again at a delayed point between 72 and 120 hours after placement. Interpretation of results is based on the appearance of redness and/or papules and/or a plaque in the shape of the chamber. Papular ($\geq$3 severity) reactions at the site of testing are common in nickel allergy in children, and they can be associated with idiopathic systemic hypersensitivity. If the testing result is negative but clinical history supports Ni-ACD, a late reading should be considered 7 to 10 days after the patch test application. There is a US Food and Drug Administration–approved series of 36 patches (T.R.U.E. Test; SmartPractice, Phoenix, AZ) that contains nickel at 200 $\mu g/cm^2$ nickel sulfate, which corresponds to 160 μg of nickel per patch. In pediatrics, standardized comprehensive patch testing is often custom tailored by history, and testing is performed with nickel sulfate hexahydrate 2.5% in petrolatum, as would be found in the American Contact Dermatitis Society Core series.[4,53] Broad-metal contact allergy screening should be performed when multiple metals are suspected as the potential source of contact dermatitis. This screening can be accomplished by using an epicutaneous metal contact allergy panel containing nickel, gold, titanium, copper, cobalt, zinc, and more than a dozen other metals.

Although children with obvious nickel allergy usually do not need confirmatory patch testing for nickel, they may need testing for other metal allergens when metal appliances for dental work or implants are needed.[68,69] In particular, the Nuss procedure, which is a placement of metal rods for the repair of pectus excavatum, has been associated with complications in patients with metal allergy, especially to nickel. Consequences include extensive granulation tissue formation, localized edema, dermatitis, lymphadenopathy, pleural effusion, and inflammation and/or infection, which may require removal of stainless steel rods in some cases.[70,71] Because of the potential consequences of undiagnosed Ni-ACD in such patients, surgeons performing the procedure often refer patients for patch testing to nickel and other metals before the procedure.[72] Stainless steel discs provided by the manufacturer are suboptimal to screen for metal allergy and Ni-ACD in this setting; it is more prudent to proceed with patch testing by using the extended metal series.[73] Titanium bars can be used safely in patients with Ni-ACD if they are identified before surgery as having no previously reported allergic events.[70]

PREVENTION OF NI-ACD

Avoidance of Nickel Exposure in Childhood

Ni-ACD is a threat to pediatric public health that persists as a problematic skin disease into adulthood. Ni-ACD is the most common cutaneous allergy and involves lifelong hazards that can affect people's lives both personally and professionally.[74] Common cutaneous nickel-containing items include earring posts, belt buckles, jewelry, zippers, snaps, clasps, grommets, electronics, coins, keys, paper clips, chairs, braces, and implants.[2,24,45,75–77] To reduce the risk and severity of Ni-ACD, avoidance of skin contact with nickel is critical. According to European reports, earrings appear to be the most common source of elicitation of Ni-ACD, providing credence to take preventive and economic measures. The United States should heed the European lead to reduce nickel release from common contacts in children to serve and protect population health. Using the handout in Table 2, parents can identify sources of high-release nickel in their children's lives. The purchase of items with no nickel or with a low release of nickel can be guided by the use of the dimethylglyoxime test, which indicates a pink or red color on exposure to a nickel-releasing metallic item. Currently, because of the lack of labeling of low–nickel-release or nickel-free metal items, parents can screen metal objects for nickel release using such test kits, which can be purchased on medical Web sites (eg, https://www.delasco.com/spot-test-for-nickel/ and

https://athenaallergy.com/pages/how-to-test-for-nickel-using-nickel-alert-dimethylglyoxime-test).[78] However, it would be more ideal if labeling of low–nickel-release or nickel-free items was available for parents.

Reduction in Dietary Nickel Exposure

Withdrawal diets in children cannot be recommended because of inadequate pediatric data and risk of malnutrition with a limited diet.[50,79,80] Data on the use of low-nickel diets in children are lacking.[51,81,82]

Advocacy

Ni-ACD represents a significant and preventable pediatric public health burden. Regulation of nickel release in materials that comes in contact with skin can decrease both the high pediatric prevalence and treatment costs of the disease. There is a call in the United States for such regulation[2] given the high number of children affected by this disease. The American Academy of Dermatology has recently accepted a proposal in support of reduced nickel release in manufacturing.[82] Adoption of legislation similar to that in the EU by the US Congress would represent a promise for prevention by starting to reduce the nickel-related health burden.

A REVIEW OF EU POLICY

Nickel is ubiquitous, and people are exposed to it primarily via metal objects throughout their lifetimes. Preventive models of safer exposures, or those less likely to trigger Ni-ACD, have been demonstrated by other countries to be medically and economically beneficial. The EU Nickel Directive of 1994 (approved June 30, 1994, and in full effect June 2001) regulated the method for measuring nickel release onto human skin and established regulations for nickel allowed to be released onto exposed skin over time, including for watches, buttons, zippers, and now mobile phone cases.[83] The EU directive was born from the original work in Denmark, where the Nickel Directive was designed to limit the maximum release of nickel in contact with human skin to an amount less than 0.2 μg/cm^2 per week for posts inserted into pierced skin and not more than 0.5 μg/cm^2 per week for products with prolonged and direct skin contact.[83,84] The European standard EN 1811:2011+A1:2015 is a standardized testing system that is approved by the EU to measure the potential amount of nickel release under the conditions of direct and prolonged contact with the skin. Articles, such as those used for earrings in children, should not release nickel more than 0.2 μg/cm^2 per week (by EN 1811 testing) to prevent children from becoming allergic to nickel or having a dermatitis reaction if they are already allergic to nickel. This nickel-release rate is for the parts of earrings that are in contact with the skin and within the pierced part of the ear.[4,83] Germany and Sweden joined in the legislation and eventually Korea and China did as well.[83]

Because the rate of release of nickel (and not nickel content itself) is important and relevant in determining whether there is a risk for Ni-ACD, articles may contain nickel but not cause a dermatitis reaction. For example, surgical stainless steel (grade 316L), which contains 10% to 15% nickel and does not release nickel more than 0.2 μg/cm^2 per week (by using EN 1811 testing), is therefore regarded as appropriate for use in articles in direct and prolonged contact with the skin. The American Section of the International Association for Testing Materials Standard Consumer Safety Specification for Adult Jewelry (designation: F2999-13) lists surgical stainless steel (typically containing 10%–15% nickel) as one of the "approved materials for adult body-piercing jewelry."[4,84,85]

The effect of the Danish decree was a drastic decrease in pediatric nickel sensitization from 24.8% to 9.2%.[85] Reduction in Ni-ACD after Denmark's Nickel Directive resulted in cost savings that grew to more than $2 billion (US dollars) over the 2 decades after implementation.[4] The EU followed the commanding lead of the Danish dermatologists who worked with the Danish ministry to advance this innovative health directive. In 2006, the Nickel Directive was incorporated into the EU regulation of toxins, which is called Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH).[84] After this regulation, there was a significant reduction of Ni-ACD in patients younger than 30 years studied in European countries.[83] National databases involving 180 390 patients with suspected ACD reveal an approximately 10% reduction in Ni-ACD in young women, specifically from the following 4 countries, in the years 1985–2010: Denmark, Germany, Italy, and the United Kingdom (2004–2010 only).

REACH is a complex bill that outlines industry obligations regarding 30 000 chemicals. REACH is far more "reaching" than is the US counterpart, the Toxic Substances Control Act (TSCA) of 1975,[86] which regulates chemicals but does not differentiate toxic from nontoxic chemicals. The TSCA was supplanted by the Chemical Safety for the 21st Century Act, introduced in the Senate in 2015 and passed in the House of Representatives in May 2016. Although the TSCA required the Environmental Protection Agency (EPA) to consider least burdensome chemical regulations for industry, the Chemical Safety for the 21st Century Act tasks the EPA to focus on unreasonable risk to human health and the environment; however, unfortunately, this may not apply to

jewelry and cosmetics.[86–88] Although the EPA acknowledges the hazards of nickel as a cause of ACD, no current ruling restricts nickel exposures in childhood; however, this regulatory foundation has room to act to reduce risk for Ni-ACD in children.[86–89] The United States stands to improve collective health status and lower related medical costs if it were to follow Denmark's lead and the EU model in protecting the public from the hazards of high nickel exposure.

Stakeholders may note that the nonprofit organization Nickel Producers Environmental Research Association does support the elimination of high-release nickel alloys and plating used in products with dermal contact such as jewelry and electronics.[7,90] US legislators should advance evidenced-based policies to adopt a twofold guideline: (1) adoption of the EU guidelines on nickel release in manufacturing and (2) adoption of a policy to avoid usage of nickel in plating in household electronic devices. If the United States can incorporate safety directives and sound recommendations regarding nickel production and usage, as has been done in the EU, then the population can achieve significant reductions in Ni-ACD in the next 2 to 3 decades.

RECOMMENDATIONS

The following are recommended to reduce the US pediatric burden of Ni-ACD:

1. To minimize nickel-induced ACD in children, use of nickel in the manufacture of items that have direct or prolonged contact with the skin (eg, jewelry, electronic devices, toys, etc) should be limited. Regulations similar to the EU Nickel Directive that limit the weekly allowable release of nickel to less than 0.5 μg/cm^2/week should be adopted.
2. Additional safety and toxicity studies are needed to better understand the complex relationship between nickel exposure and population health.
3. Companies and industries using metal in products should voluntarily create labeling for low–nickel-release products and Web-based resources to identify those items in the United States that follow EU legislation guidelines, allowing individuals who are nickel allergic to shop more wisely. Ideally, the development of trustable resources for those with Ni-ACD can be met through physician and industry partnership to develop educational resources about nickel allergy that can be easily understood and accessed by children, parents, and teachers.
4. Physicians and other health care providers can support the reduction of Ni-ACD by encouraging parents to request that posts for piercings in their children's ears be made of surgical-grade steel with low nickel release, per EU standards. It is recommended that all individuals who perform piercing services mention Ni-ACD as a potential complication of piercing.
5. Nickel allergy can be genetic; therefore, physicians and other providers should consider educating at-risk groups to avoid nickel-based body piercings. There is further genetic reason to believe that children from families with a history of Ni-ACD would benefit from reduced exposure in childhood through the universal use of low–nickel-releasing jewelry.
6. It is likely that most children would benefit from lower exposure to such contact, even in the absence of family history of Ni-ACD, because such family history is only present in approximately half of cases of documented disease.
7. If orthodontic metal braces are anticipated, families should consider delaying ear piercing until after dental work is completed.
8. Until such legislation can be passed, voluntary manufacturer reduction of nickel-releasing metal in children's clothing and close contacts, including grommets, button flies, belt buckles, school chairs, and tables, aimed for use by children would reduce Ni-ACD disease burden. Reporting of voluntary reduction on labels and on public Web sites would help parents of children and adolescents with Ni-ACD identify hypoallergenic metal objects, further enhancing reduction of disease symptomatology and burden.

CONCLUSIONS

Ni-ACD is a common chronic dermatitis with detrimental effects on children now and as they progress into adulthood. The burden of symptoms and cost is high. The United States can act on EU data revealing that legislation to limit exposures in childhood, especially with earrings, can impact the prevalence and potentially the severity of disease. Until and even if legislation is available, pediatricians can help patients by identifying the allergy early and intervening with a plan of prevention and care of disease.

LEAD AUTHORS

Nanette B. Silverberg, MD, FAAP, FAAD
Janice L. Pelletier, MD, FAAP
Sharon E. Jacob, MD, FAAP, FAAD
Lynda C. Schneider, MD, FAAP

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ABBREVIATIONS

ACD: allergic contact dermatitis
EPA: Environmental Protection Agency
EU: European Union
NACDG: North American Contact Dermatitis Group
Ni-ACD: nickel allergic contact dermatitis
REACH: Registration, Evaluation, Authorization, and Restriction of Chemicals
TSCA: Toxic Substances Control Act

Address correspondence to Nanette B. Silverberg, MD. E-mail: nanette.silverberg@mountsinai.org

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Nickel Allergic Contact Dermatitis: Identification, Treatment, and Prevention

Nanette B. Silverberg, Janice L. Pelletier, Sharon E. Jacob, Lynda C. Schneider and SECTION ON DERMATOLOGY, SECTION ON ALLERGY AND IMMUNOLOGY

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