Nickel Allergic Contact Dermatitis in Children

Sharon E Jacob MD
Founder, CEO, Dermatitis Academy
Professor, Dermatology,
Loma Linda University
Disclosures

Discussing a non-FDA approved procedure
- Patch testing in children and comprehensive testing in general

Founder and CEO, Dermatitis Academy. Served as an independent investigator on the safety and efficacy of T.R.U.E. Test™ (Smart Practice; Phoenix, AZ) panels 1.1, 2.1, 3.1 in children and adolescents, Pediatric Research Equity Act (PREA-1) trial and now serves as an investigator on PREA-2. Consultant for Johnson &Johnson. Speaker Caribbean Derm Society, AAAAI, ACAAI, AAOM Primary investigator, Society for Pediatric Dermatology Pilot project: Pediatric Contact Dermatitis Registry Project at Loma Linda U. http://dermatitisacademy.com/research/
2004

• Became aware 10 years had passed since European Union adopted Nickel safety regulation and Nickel sensitization in US was on the rise
  – NACDG patch tested 25,626 US/Canadian pts found a steady increase in Ni sensitivity from 14.5% in 1992 to 18.8% in 2004 (P < 0.0001).
  – Directive lowered rates of sensitization in Danish children 0-18 y, from 24.8% in 1992 to 9.2% in 1998
• Nickel directive a good idea in the US!
  – Set out to document prevalence of nickel in the US Children
2004 Literature Review- Pediatric CD

Contact Sensitization + Patch Test

USA
Weston et al. 20.3% (314, 6mos-18yo)*
Bruckner et al. 24.5% (95, 6mos-5 yo)^

Denmark
Mortz et al. 15.2% (1501, 12-16 yo)

Portugal
Barrios et al 13.3% (562, 5-14 yo)

Allergic Contact Dermatitis + Patch Test & Clinical Relv

<table>
<thead>
<tr>
<th>Country</th>
<th>Sample Size</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>(96)</td>
<td>54%</td>
</tr>
<tr>
<td>Spain</td>
<td>(141)</td>
<td>50%</td>
</tr>
<tr>
<td>France</td>
<td>(337)</td>
<td>67%</td>
</tr>
<tr>
<td>Italy</td>
<td>(1094)</td>
<td>52.1%</td>
</tr>
<tr>
<td>Germany</td>
<td>(285)</td>
<td>52.6%</td>
</tr>
<tr>
<td>Germany</td>
<td>(2175)</td>
<td>49.7%</td>
</tr>
<tr>
<td>UK</td>
<td>(191)</td>
<td>41%</td>
</tr>
<tr>
<td>Brazil</td>
<td>(102)</td>
<td>56%</td>
</tr>
<tr>
<td>France</td>
<td>(114)</td>
<td>43%</td>
</tr>
<tr>
<td>Austria</td>
<td>(79)</td>
<td>49%</td>
</tr>
<tr>
<td>Belgium</td>
<td>(70)</td>
<td>48.6%</td>
</tr>
<tr>
<td>UK</td>
<td>(114)</td>
<td>54%</td>
</tr>
</tbody>
</table>

*1986 – Finn children are as likely as adults
^2000- TRUE
Contact Sensitization - Unaffected

- **USA**
  - Weston et al. ['86] **20.3%** (314, mos-18yo)*
    - Nickel: 24/314 (7.6%) [Finn]
  - Bruckner et al. ['00] **24.5%** (95, 6mos-5 yo)
    - Nickel: 11/85 (12.9%) [TRUE test]
<table>
<thead>
<tr>
<th>The International Top 10 – Pediatric</th>
<th>2008 NACDG 2001-4 Children</th>
<th>2014*</th>
<th>2008 UM – UPenn Pede Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td><strong>28.3% (1)</strong></td>
<td>[26.2]</td>
<td>17.5% (1)</td>
</tr>
<tr>
<td>Fragrance Mix I</td>
<td>5.1 % (6)</td>
<td>[5.0]</td>
<td>6.3% (11)</td>
</tr>
<tr>
<td>Cobalt</td>
<td>17.8 (2)</td>
<td>[8.7]</td>
<td>8.8% (7)</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>15.4% (3)</td>
<td>[ - ]</td>
<td>12.5% (2)</td>
</tr>
<tr>
<td>Myroxylon pereirae</td>
<td>3.9% (7)</td>
<td>[5.7]</td>
<td>11.3% (3)</td>
</tr>
<tr>
<td>Chromium</td>
<td>3.6% (10)</td>
<td></td>
<td>5.0% (13)</td>
</tr>
<tr>
<td>Neomycin</td>
<td>8% (4)</td>
<td>[6.6]</td>
<td>11.3% (5)</td>
</tr>
<tr>
<td>Lanolin</td>
<td>3.6% (9)</td>
<td></td>
<td>1.3 % (27)</td>
</tr>
<tr>
<td>Thiuram</td>
<td>1.8% (23)</td>
<td></td>
<td>1.3% (28)</td>
</tr>
<tr>
<td>Para-phenylenediamine</td>
<td><strong>2.1% (16)</strong></td>
<td></td>
<td>5.0% (14)</td>
</tr>
<tr>
<td></td>
<td><strong>56.7 CS rate</strong></td>
<td></td>
<td><strong>83% CS rate</strong></td>
</tr>
</tbody>
</table>

Nickel Allergy: Epidemiology

- Estimate >250,000 cases/yr of nickel ACD in children

Pediatric Dermatology 2015;32:779-785

641 cases!
1986-2014
Pediatric Nickel Cases in USA

- 611 cases confirmed, published
- 12 states
- >2000 cases in 2014
How many kiddos are sensitized?

- Prystowsky et al showed (1979) that 5.7% of an asymptomatic US population had been (unknowingly) sensitized to nickel. ¹
- Weston/Bruckner (1986, 2000) – 7.6% and 12.9%
- Estimate 11% (nickel sensitization rate)²
- 8,133,603 children sensitized to nickel

2. Assuming = to adults, based on LLU current Nickel Survey Gen Population Data
Nickel Allergic Contact Dermatitis Data Survey
Database of self-reporting nickel dermatitis index cases  IRB: 5150230

- Nickel #1 sensitizer for 70 years.
- Safe use guidelines in Europe since 1990s\(^2\).
  (Pre-directive prev. rate x%)  
- Similar US save $5.7 billion annually\(^3\).
- Gen adult US prev estim 10-15%  
- Gen Ped US prev estim 12.9%  
- Canvassing survey aims:  
  - Document prevalence of nickel allergy in US  
  - Encourage safer alloy use guidelines  
- Survey Launched Jan. 9, 2016:  
  - 266 (+) responses to date  
  - F2f 64/481 = 11.7%

Citations:

Slide design: Dan Bergman & Chandler Rundle
The many faces of Nickel Dermatitis – Complicating the Big Picture

- Localized

- Generalized - Systematized – ID
  - Association with AD**
Body piercing and metal allergic contact sensitivity: North American contact dermatitis group data from 2007 to 2010.


Abstract

OBJECTIVE: This study aimed to examine the association between piercing and patch test sensitivity to metals (nickel, cobalt, and chromium) in North America.

METHODS: A retrospective analysis of 9334 patients tested by the North American Contact Dermatitis Group from 2007 to 2010 was conducted.

RESULTS: Nickel sensitivity was statistically associated with at least 1 piercing (risk ratio [RR], 2.52; 95% confidence interval [CI], 2.26-2.81; P < 0.0001) and nickel sensitivity rates increased with the number of piercings (16% for 1 piercing to 32% for ≥ 5 piercings). Prevalence of nickel sensitivity was higher in females (23.2%) than in males (7.1%), but the association with piercing was stronger in males (RR, 2.38; 95% CI, 1.72-3.30; P < 0.0001) than in females (RR, 1.30; CI, 1.13-1.49; P = 0.0002). Crude analysis indicated that cobalt sensitivity was statistically associated with piercing (RR, 1.63; 95% CI, 1.40-1.91; P < 0.0001); however, stratified analysis showed that this relationship was confounded by nickel. After adjusting for nickel sensitivity, the adjusted risk ratio for piercing and cobalt was 0.78 (not significant). Chromium sensitivity was negatively associated with piercing (RR, 0.60; 95% CI, 0.48-0.75; P < 0.0001).

CONCLUSIONS: Piercing was statistically associated with sensitivity to nickel. This relationship was dose dependent and stronger in males. Cobalt sensitivity was not associated with piercing when adjusted for nickel. Chromium sensitivity was negatively associated with piercing.

PMID: 25207687 [PubMed - indexed for MEDLINE]
"Jewelry Addicts"

The "Jewelry Addict": Allergic Contact Dermatitis from Repetitive Multiple Children's Jewelry Exposures.

Silverberg NB.

Abstract

A 9-year-old girl with atopic dermatitis developed persistent plaques on the lips, hands, and fingers that were unresponsive to topical steroids. Her mother reported that she was "addicted" to costume jewelry and developed rashes in reaction to a number of adornments, ranging from rubber bracelets to costume metal jewelry and belt buckles. A careful history of jewelry exposures was taken and patch testing was performed to identify allergenic sources. Patch testing revealed allergy to nickel, gold, and thimerosal mix. The case illustrates the importance of investigating a range of different types of allergens when evaluating for jewelry sensitivity in children with frequent use of accessories, including rubber jewelry, plastics, dyed yarns, beads, metals, and ceramics. This article provides an overview of jewelry allergies and the potential allergens requiring screening.

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PMID: 27001330 [PubMed - as supplied by publisher]
Call to action!!! [http://dermatitisacademy.com/nickel-page/]
Report your allergy! Please LIKE and SHARE - we need 200! Tag 5 friends in the comments! Awareness of the epidemic is needed.

DETECT!

Even though it says it, it doesn't mean it's true!

7,958 people reached
Underwire bras (the snap back)

School Chair’s Sign - Belsito et al. Cutis

85% of nickel dermatitis hx: earlobe or umbilical rash

Direct

‘Ectopic’
Belts and generalized dermatitis (SCD) in AD

Belt Buckles—Increasing Awareness of Nickel Exposure in Children: A Case Report

Alina Goldenberg, MD, MAS, Shehla Admani, MD, Janice L. Pelletier, MD, FAAP, Sharon E. Jacob, MD

Children, especially those with atopic dermatitis, are at risk for nickel sensitization and subsequent dermatitis from metal-containing objects, namely belt buckles. We describe allergic contact dermatitis in 12 children with peri-umbilical nickel dermatitis (with and without generalized involvement) caused by dimethylglyoxime-positive belt buckles. The patients’ symptoms resolved with avoidance of the nickel-containing products.

Nickel allergic contact dermatitis (Ni-ACD) has become increasingly recognized in the pediatric population, with prevalence rates in patch-tested populations of ~25% throughout the last decade. Nickel is one of the most common causes of allergic contact dermatitis in children.

In the literature, nickel exposure in children has been linked to a wide range of materials and accessory sources, with ear piercing being highly ranged from 9 to 15 years old, mean age 12.5 years; the group included 5 males and 7 females. Information on race was available for 10 patients: 5 were white non-Hispanic, 4 were Hispanic, and 1 was Asian. Atopic dermatitis history was present in 9 patients (75%). Family history of contact dermatitis or atopic triad was not available (Table 1). Clinically, Ni-ACD presents hours to days after initial exposure; it may be confined to the site

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>12.5 (9 to 15)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Race*</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Location of nickel dermatitis</td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Peri-umbilical only</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Other*</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Concurrent atopic dermatitis</td>
<td>9 (75)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) unless stated otherwise.

* Race information missing for 2 cases.

* Other includes torso, legs, ear, and axilla.
iPad—Increasing Nickel Exposure in Children

abstract
We discuss allergic contact dermatitis to the iPad to highlight a potential source of nickel exposure in children. *Pediatrics* 2014;134:e580–e582

**AUTHORS:** Sharon E. Jacob, MD and Shehla Admani, MD
Division of Dermatology, University of California, San Diego, Rady Children’s Hospital, San Diego, California

**KEY WORDS**
allergic contact dermatitis, iPad, nickel

**ABBREVIATIONS**
ACD—allergic contact dermatitis
AD—atopic dermatitis

Generalized Reaction in Atopic

Allergic Contact Dermatitis to a Laptop Computer in a Child

Sharon E. Jacob, M.D., and Shehla Admani, M.D.
Division of Dermatology, University of California, San Diego, Rady Children’s Hospital, San Diego, California
TOYS!


Nickel and cobalt release from children’s toys purchased in Denmark and the United States.
Jensen P¹, Hamann D, Hamann CR, Jellesen MS, Jacob SE, Thyssen JP.

Author information

Abstract

BACKGROUND: Nickel is the most common allergen detected by patch testing in children. There is an increasing number of cases in children who have not had exposure to piercing. Although the clinical relevance of nickel patch test reactions in children is sometimes uncertain, continued vigilance to identify new sources of nickel exposure in this age group is important. Recent case reports have described allergic nickel contact dermatitis in children following exposure to toys, but the magnitude of this problem is unknown.

OBJECTIVE: The aim of this study was to evaluate nickel and cobalt release from children’s toys.

METHODS: We purchased 212 toys in 18 different retail and online stores in the United States and Denmark. Nickel and cobalt release was tested using the dimethylglyoxime and cobalt screening spot tests.

RESULTS: A total of 73 toys (34.4%) released nickel, and none released cobalt.

CONCLUSIONS: Toys are a commonly overlooked source of nickel exposure and sensitization. Therefore, dermatologists, allergists, and pediatricians should consider the role of toys in their evaluation of children with dermatitis, and the parents of children with positive nickel patch test reactions should be told that toys may release nickel and be a potential chemical source in the manifestation of allergic contact dermatitis.

PMID: 25384229 [PubMed - indexed for MEDLINE]


Nickel released from children’s toys is deposited on the skin.
Overgaard LE¹, Engebretsen KA¹, Jensen P¹, Johansen JD¹, Thyssen JP¹.

Author information
"Mint" Condition: Contact Dermatitis in an Adolescent Numismatist.

Cotton CH¹, Admani SE², Jacob SE³, Krakowski AC¹,⁴.

Author information

Abstract

Allergic contact dermatitis (ACD) is common in children and adolescents. A history of persistent rash despite appropriate treatment should raise suspicion of ACD. We present the case of a 16-year-old boy with chronic dermatitis suspected of being a possible nickel allergy. He and his mother denied known common exposures. Patch testing confirmed allergies to multiple metals and several preservatives. A detailed social history revealed that the patient was an avid coin collector. Information about hobbies and activities should be elicited in any patient in whom ACD is suspected to determine exposures they may not initially have considered relevant. This case highlights the importance of pre- and posttest counseling and exposure history.

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PMID: 26758091 [PubMed - in process]
Nickel in coins

- Nickel is appealing due to price, color, shiny surface, weight, corrosion resistance, easy to stamp and recycle.
- Nickel contamination of the fingers has been found to be in direct proportion to the exposure time of rubbing coins (10 sec - 10 min).
- Blinded multi-center provocation study showed hand eczema flares in a majority of nickel allergic patients after stacking coins for 4 hours, with higher rates and severity of dermatitis with increased nickel release.
- All Swedish coins from 2015 nickel-free.
- In the US, 3/5 coins are DMG +
  - Piercings, coins, keys and toys – pediatric sources.

Slide courtesy of Dr. Jennifer Chen, MD
Nickel released from children's toys is deposited on the skin.

Overgaard LE¹, Engebretsen KA¹, Jensen P¹, Johansen JD¹, Thyssen JP¹.
In one recent study, SNAS alone was identified in up to 6% of patients presenting to allergy clinics in Europe, implying that SCD may be under-identified in the dermatitis population.\(^1\)

A meta review by Jensen specifically assessed elicitation of SCD due to nickel ingestion, and found that 1% of those sensitized to nickel react to the nickel content of a “normal” diet, defined as 0.22mg, 0.35 mg, or 0.53mg...a dose-response relationship was revealed showing 10% of nickel sensitized patients responding to exposures between 0.55 mg and 0.89 mg.\(^2\)

Systemic Nickel Allergy Syndrome (SNAS)

- SNAS often presents with a host of systemic symptoms including heartburn, abdominal pain, nausea, vomiting, constipation, abdominal distension rhinitis, asthma, headache, chronic fatigue syndrome, arthralgia, fibromyalgia, and fever.
- SCD may also be a misleading term, because skin contact with nickel is not a requirement for disease elicitation though reactivation of previous nickel contact sites may be seen, clinical presentation also includes generalized skin manifestations, such as urticaria and eczema.
*Pollutants [nickel (P=0.0002)] in conjunction with climate factors may differentially impact eczema prevalence and severity, some with apparent harmful effects.


Association between small particle air pollution, climate and childhood eczema prevalence and severity: a population-based study.

Kathuria P1, Silverberg JI2,3.
Association between small particle air pollution, climate and childhood eczema prevalence and severity: a US population-based study.

Kathuria P¹, Silverberg J²,³.

Author information

Abstract

BACKGROUND: We sought to determine the relationship between childhood eczema, climate and environmental pollutants.

METHODS: We analyzed data from the 2007-2008 National Survey of Children’s Health including a representative sample of 91,642 children age 0-17 years and the 2006-2007 Environmental Protection Agency measurements of carbon monoxide (CO), nitrate (NO₃⁻), nitrogen dioxide (NO₂), organic carbon (OC), sulfate (SO₃²⁻), sulfur dioxide (SO₂), particulate matter ≤2.5 micrometer (PM-2.5) and <10 micrometer (PM-10) and tropospheric ozone levels, and the National Climate Data Center measurements of relative humidity (%), issued UV index, outdoor air temperature and precipitation levels.

RESULTS: In multivariate survey logistic regression models controlling for age, sex, race/ethnicity, household income, US birthplace and history of moving to a new location, eczema was associated with higher mean annual NO₂ (P=0.008), SO₂ (P=0.006), SO₃ (P=0.0002), arsenic (P=0.0007), nickel (P=0.0002), lead (P=0.03), vanadium (P<0.0001) and zinc (P=0.003), but lower NO₃ (P=0.002), OC (P=0.03), PM-2.5 (P=0.006), cadmium (P<0.0001), copper (P=0.004) and potassium (P<0.0001). In contrast, moderate-severe eczema was associated with higher NO₃ (P=0.03), OC (P=0.008) and PM-2.5 (P=0.01), copper (P=0.04), lead (P=0.008) and zinc (P=0.01), but lower CO (P=0.03). Principal component analysis was used and identified 4 combinations of pollutants and climate factors occurring in the US, of which 1 was associated higher prevalence and 2 were associated with lower prevalences of eczema (P<0.05).

CONCLUSIONS: Pollutants in conjunction with climate factors may differentially impact eczema prevalence and severity, some with apparent harmful effects. This article is protected by copyright. All rights reserved.
Pollution and Nickel… 1993 Norway

- **Sør-Varanger Municipality in Finnmark County** [north of Norway] receives much **air-borne pollution from domestic industry** and from the metallurgic industry on the Kola peninsula in North-Western Russia.
- **Investigated indirect parameters of morbidity caused by asthma- eczema** by analyzing data on drug consumption and hospital admissions.
- In Sør-Varanger there is **high consumption of corticosteroids for dermatological use.**
- Consumption of **anti-asthmatic drugs** and number of admissions to hospital for asthma and eczema were no higher than expected.
- We suspect that air-borne pollution, particularly the **heavy metal nickel**, increases the prevalence and perhaps worsens the degree of eczema in Sør-Varanger.

Sunde HG1, Holtedahl KA. Air pollution, eczema and asthma in Sør-Varanger. Is the high consumption of corticosteroid ointments caused by increased tendency for eczema? Tidsskr Nor Laegeforen. 1993 Jan 20;113(2):218-21.
Investigating impact of Ni-ACD on AE

- 73,941,848 children in US
- ‘Atopic eczema is a very common skin disease. It affects between 8.7% to 18.1% of all infants and children’.*
- 6,432,940 - 13,383,474 children in US w/AE
- Estimate ~11% (nickel sensitization rate)
- 8,133,603 children sensitized to nickel

Nickel and AD

- Of 134 children with AD, 33.8% (n = 45) had at least 1 positive reaction.
- #1 was nickel sulfate (NS) (37.8%, 17/45), followed by methylchloroisothiazolinone (20.0%, 9/45) and thimerosal (15.6%, 7/45).
- Scoring Atopic Dermatitis (SCORAD) significantly higher in NS-group (P = 0.036).
- Patients with NS sensitization had moderate-severe AD more frequently than those without any reaction (P = 0.020).
- When the SCORAD score was evaluated in detail, extent of eczema, score of sleep loss, and pruritus were significantly >> with NS sensitization than those without any reaction (P = 0.002, P = 0.001, & P = 0.002, respectively).
- NS sensitization should be considered for children with severe AD or larger extent of eczema and trunk involvement.


• Atopic dermatitis (AD) double-hit phenomenon
  – ‘unknown environmental component’
    • Staph aureus in AD reported > 20y ago
    • Staph relationship to AD has been elusive
      – Biofilm formation by AD-associated staphylococci major role in the occlusion of sweat ducts and leads to inflammation and pruritus.
  – a genetic abnormality likely filaggrin gene.
Epidermal barrier crucial for development of sensitization and elicitation of ACD.

Recently, the key role of filaggrin (FLG) proteins in maintaining an effective skin barrier against the external environment has been demonstrated [20].

A positive association between FLG mutations and contact sensitivity (CS) to nickel was found among German adults [21], but could only be confirmed in Danish adults without ear piercings [22].

Furthermore, FLG mutation carriers reported ACD to nickel at a significantly younger age than controls with normal filaggrin, and they also displayed stronger patch test reactivity [23].

Nickel ions, like many other metal ions, are electrophilic in nature, which causes reactivity toward certain protein elements. It was hypothesized that those subjects who have FLG mutations are more susceptible to the acquisition of CS to nickel following topical exposure.

This was supported by a study showing strong nickel chelation by the histidine-rich filaggrin proteins.

CS to metals has been found to have a significant association with AD in both children and adults, probably due to the compromised chelating functions of AD skin.

From these finding concluded that in AD, there may be an opportunity for more potent/easier access of chemical allergens to the viable epidermis, which could enhance the acquisition of CS.

- The combined carrier frequency of FLG null mutations was 8.1%. Nickel, fragrance and contact sensitization to at least one allergen were not associated with FLG null mutations.
- A crude analysis on women who did not have ear piercings revealed a positive association between FLG null mutations and nickel sensitization [8.3% vs. 2.4%; odds ratio (OR) 3.71, 95% confidence interval (CI) 0.73-18.96] as well as between FLG null mutations and allergic nickel dermatitis (8.3% vs. 1.3%; OR 6.75, 95% CI 1.17-38.91).
- FLG mutation status and atopic dermatitis were positively associated with neomycin or ethylenediamine sensitization.
- This study suggests that FLG null mutations may be a risk factor for the development of nickel sensitization.
- However, ear piercing was a much stronger risk factor in our general population and we could therefore identify a positive association only in women without ear piercings. Contact sensitization to specific chemicals is related to treatment exposure.
The Staph Biofilm

- Sessile bacterial communities encased in extracellular matrix w/well-developed communication system
- Regulate bacterial growth and metabolism
- Confer resistance to antimicrobials and to host inflammatory cells
- Alter host metabolism

- Nickel allergy confirmed in atopic patients - excluded in healthy volunteers using patch testing.
- Infection by S. aureus was tested in atopic patients and healthy volunteers by use of API Staph system.
  - IgE for staphylococcal enterotoxin A and B measured.
  - Secretion of IFN-γ, IL-2, IL-13 by PBMC under nickel sulfate and the enterotoxins A and B stimulations were studied with ELISpot.

- **Incr. # infections by S. aureus in atopic patients with nickel allergy** in comparison to atopic patients and healthy volunteers W/O nickel allergy.

- The **elevated secretion of IL-2 under nickel sulfate stimulation** in vitro was **exclusively** found in atopic patients with nickel allergy infected by S. aureus.

- Suggest nickel allergy and infection by S. aureus are linked in atopic dermatitis.
Why the patch tests might be negative - “Hypo-responsive state”

- Gene expression and immunohistochemistry studies were performed on 10 patients with AD and 14 patients w/o AD patch tested with nickel, fragrance, and rubber.

- Although many inflammatory products (ie, matrix metalloproteinase 12/matrix metalloproteinase 1/S100A9) were upregulated in both groups, higher-magnitude changes & upregulation IFN responses were evident only in the non-AD group.

- Stratification by allergen showed decreased expression of immune, TH1-subset, and TH2-subset genes in nickel-related AD responses, with increased TH17/IL-23 skewing. Rubber/fragrance showed similar trends of lesser magnitude. Negative regulators showed higher expression in patients with AD.

- Through contact sensitization, our study offers new insights into AD. Allergic immune reactions were globally attenuated and differentially polarized in patients with AD, with significant decreases in levels of TH1 products, some increases in levels of TH17 products, and inconsistent upregulation in levels of TH2 products.

- The overall hyporesponsiveness in skin from patients with background AD might be explained by baseline immune abnormalities, such as increased TH2, TH17, and negative regulator levels compared with those seen in non-AD skin.

“Intradermic test is almost never used on clinical practice, but it may be utilized in case of doubtful patch test reactions, either to identify false-positive reactions or to confirm a clinical suspicion of nickel dermatitis in patients with negative patch tests. It can also reveal the degree of sensitivity with different titrations, which can’t be done with standard patch tests.”

Fernanda Torres, Maria das Graças, Mota Melo, Antonella Tosti Management of contact dermatitis due to nickel allergy: an update. Clinical, Cosmetic and Investigational Dermatology 2009:2 39–48

Why are we seeing this in children?

- 3471 Danes (18-69 years of age) - questionnaire about general health, and underwent patch testing and filaggrin genotyping.
- Mean number of years at risk of developing nickel dermatitis was significantly lower for the filaggrin null genotype than for the wild-type genotype when ear piercing status was considered.
- In positive patch test readings, the proportion of null mutants increased with increasing reaction strength.
- Filaggrin null mutations may lower the age of onset of nickel dermatitis.
- The hypothesis that ear piercings obscure the effect of filaggrin null mutations on the development of nickel allergy in statistical analyses was supported.
- An association between the null genotype and increased nickel sensitivity was indicated by patch test reading and questionnaire data.
Summary ACD in AD

• Pts with atopic dermatitis have increased penetration of the epidermis by allergens, which increases their risk of contracting contact dermatitis.

• Strong correlation between having a genetic mutation in Filaggrin and increased skin permeability, and a study showed that carriers for Filaggrin had a higher chance of having allergic nickel dermatitis.

• Increased exposure to topical products.

• Immuno-dependent ‘protection’?, where patients expressing the most severe symptoms of atopic dermatitis may have a reduced reactivity on patch testing.

• Important to patch test patients with atopic dermatitis for allergens found both in metals and in topicals, as patients who have atopic dermatitis as children often contact allergic contact dermatitis.
  – Duplicate testing – double delayed and the 30min take down
  – ‘Intradermic’

** Controversy in the literature – speak to this
Why are the reported #s so low?

- Consumers *self diagnose*
- Clinical providers great at dx localized nickel
- Nickel allergy is going *undetected* – “eczema-like”
It’s a pediatric wellness issue

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**INTENT FOR CLINICAL REPORT, POLICY STATEMENT, OR TECHNICAL REPORT**

<table>
<thead>
<tr>
<th>Authoring Group/s:</th>
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</thead>
<tbody>
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<tr>
<td>Title of Document:</td>
<td>Nickel Allergy and Contact Dermatitis in Children</td>
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- **Check here if this document is NEW and choose the following format/s that apply:**
  - [ ] Clinical Report (CR) Guidance for the Clinician in Rendering Pediatric Care
  - [x] Policy Statement (PS) Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children
  - [ ] Technical Report (TR)* Background information to support a clinical report or policy document

*If supporting a CR or PS, as opposed to a stand-alone TR, it is anticipated that the TR would be published concurrently with the respective document in the same or mutually referenced publication.
The American Academy Pediatrics

Position statement is coming…

You can’t tell an adult they can’t pierce and smoke… but you can protect a child.
Thank you!

- 86 Japanese AD patients 3 university hospitals, consisting of 55 extrinsic & 31 intrinsic AD patients.
- Patch testing - nickel, cobalt, and chrome, in parallel with other 14 metals.
- FLG mutations were analyzed in 49 patients (extrinsic, 29; intrinsic, 20).
- In 17 patients (extrinsic, 12; intrinsic, 5), sweat was collected from the forearms by exercise, and the concentration of nickel was fluorometrically measured.
- Nickel, cobalt, and chrome were the major positive metals.
- Intrinsic AD showed significantly higher percentages of positive reactions than extrinsic AD to nickel (intrinsic 41.9% vs extrinsic 16.4%, P=0.019) and cobalt (38.7% vs 10.9%, P=0.005).
- There was no significant difference between FLG mutation-bearing and non-bearing patients.
- The concentration of nickel was higher in the sweat of intrinsic AD than extrinsic AD patients (333.8 vs 89.4ng/g, P=0.0005) and inversely correlated with serum IgE levels.
- Nickel and cobalt allergy may be involved in intrinsic AD. Given that the metals are excreted through sweat, intrinsic AD might be exaggerated by highly metal-containing sweat.
The nickel dose-response relationship by filaggrin genotype (FLG).

- On skin contact, nickel accumulates in the stratum corneum, likely binds proteins and amino acids. Probable contributor is filaggrin, which binds nickel avidly.
- Filaggrin gene (FLG) null mutations lead to a complete lack of filaggrin production from the affected allele, and have been associated with an increased risk of nickel contact sensitization in German and Danish adults.
- Thirteen nickel-sensitized female patients, seven heterozygous mutation carriers and six non-mutation carriers (genotyped for R501X, 2282del4, or R2447X), were patch tested and performed a repeated open application test (ROAT) with a nickel sulfate dilution series.
- Elicitation threshold level for nickel is independent of FLG null mutation single-allele carrier status.

- Allergic contact dermatitis prevalent dermatological problem ~ 7% of the general population.
- Impaired skin barrier function facilitates the penetration of contact allergens and irritants into the epidermal layer and is regarded as an important cofactor promoting the process of allergic contact sensitization.
- Filaggrin is crucial for the maintenance of the skin barrier function.
- Assess the impact of FLG on allergic contact sensitization and plausible intermediate traits, the two prevalent FLG mutations R501X and 2282del4 were typed in 1,502 individuals of the KORA C population-based cohort with extensive dermatologic phenotyping.
- Associations of FLG mutations with AE could be replicated.
- Association with contact sensitization to nickel and contact sensitization to nickel combined with intolerance to fashion jewelry, but not with other contact allergens, was observed.
- FLG deficiency may also represent a risk factor for contact sensitization to allergens.
Belt Buckles—Increasing Awareness of Nickel Exposure in Children: A Case Report

Alina Goldenberg, MD, MAS\textsuperscript{a}, Shehla Admani, MD\textsuperscript{b}, Janice L. Pellegrin, MD, FAAP\textsuperscript{c}, Sharon E. Jacob, MD\textsuperscript{d}

Children, especially those with atopic dermatitis, are at risk for nickel sensitization and subsequent dermatitis from metal-containing objects, namely belt buckles. We describe allergic contact dermatitis in 12 children with peri-umbilical nickel dermatitis (with and without generalized involvement) caused by dimethylglyoxime-positive belt buckles. The patients' symptoms resolved with avoidance of the nickel-containing products.

Nickel allergic contact dermatitis (Ni-ACD) has become increasingly recognized in the pediatric population, with prevalence rates in patch-tested populations of ~25\% throughout the last decade.\textsuperscript{1,2} Nickel is one of the most common causes of allergic contact dermatitis in children.

In the literature, nickel exposure in children has been linked to a wide range of materials and accessory sources, with ear piercing being highly ranged from 9 to 15 years old, mean age 12.5 years; the group included 5 males and 7 females. Information on race was available for 10 patients: 5 were white non-Hispanic, 4 were Hispanic, and 1 was Asian. Atopic dermatitis history was present in 9 patients (75\%). Family history of contact dermatitis or atopic triad was not available (Table 1). Clinically, Ni-ACD presents hours to days after initial exposure; it may be confined to the site

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>12.5 (9 to 15)</td>
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<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (58)</td>
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<tr>
<td>Race\textsuperscript{a}</td>
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<tr>
<td>White, non-Hispanic</td>
<td>5 (42)</td>
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<tr>
<td>Hispanic</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (8)</td>
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<tr>
<td>Location of nickel dermatitis</td>
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<tr>
<td>Generalized</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Peri-umbilical only</td>
<td>1 (8)</td>
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<tr>
<td>Other\textsuperscript{b}</td>
<td>3 (25)</td>
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<tr>
<td>Concurrent atopic dermatitis</td>
<td>9 (75)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) unless stated otherwise.

\textsuperscript{a} Race information missing for 2 cases.

\textsuperscript{b} Other includes torso, legs, ear, and axilla.