The existence of systematized nickel contact dermatitis (SCD) in patients with atopic dermatitis (AD) and the association with sustained nickel exposures continues to be controversial in the literature, due to both a paucity of controlled trials and conflictual information.

There are several factors impacting nickel sensitization in atopic eczema, which involve both the environment and genetics.

An aspect of the environmental component concerns formation of a biofilm by *Staphylococcus aureus*, leading to sweat duct plugging and potentiation of inflammation and pruritus in AD affected skin.

**STAPHYLOCOCCUS BIOFILM AND INTERACTION WITH METALS**

Biofilms are a bacterial-based community enclosed by an extracellular matrix that promotes bacterial growth and alters defensive host mechanisms. The bacteria found within these biofilms tend to be more resistant to antibiotics and host defenses, as leukocytes and antibiotics have greater difficulty penetrating and impacting the bacteria (Staphylococcus), thus allowing supercolonization. It is known from research in chronic wound care that biofilms augment the inflammatory response, and indeed is also the case in AD.

The relationship between *Staphylococcus aureus* AD and nickel allergy is further complicated because nickel and other metals have an effect on the phagocytic activity of bacteria. One of the roles of human polymorphonuclear leucocytes (PMN) is phagocytosis of bacteria. One study exposed various metals to these PMNs in vitro, including cobalt, nickel, and chromium. Nickel was found to decrease the number of bacteria phagocytosed, therefore leading to a persistence of *S. aureus* on the skin, forming biofilms, and thus further aggravating the atopic dermatitis condition.

A study done by Gonzalez and Jensen revealed that *S. aureus* has a role of incorporation of metals and placing them into its cellular compartments. They highlighted that polyphosphate bodies are responsible for binding to and sequestering large amounts of nickel during *S. aureus* infection. Furthermore, recent studies indicate that *Staphylococcus aureus* carries a trace metal transporter, the Opp1 ABC transporter. This unique nickel transporter

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**BY SHARON E. JACOB, MD AND NIKOLETA BRANKOV, MD**

"The compromised chelating functions of AD and the decreased acidification that are associated with filaggrin deficiency lead to enhanced penetration of nickel ions through a histidine depleted stratum corneum."
has a significant role in the persistence of *S. aureus* infection in AD patients.\(^8\)

**FILAGGRIN AND NICKEL AND STAPHYLOCOCCUS**

Evidence suggests that the genetic component in a subset of AD centers on a mutation in the filaggrin (FLG) gene.\(^2\) The link between nickel allergy and AD might be explained by the shared association with loss-of-function mutation in the filaggrin gene. The compromised chelating functions of AD and the decreased acidification that are associated with filaggrin deficiency lead to enhanced penetration of nickel ions through a histidine depleted stratum corneum.\(^9\) Furthermore, it is known that filaggrin degradation products inhibit *Staphylococcus* growth, and therefore in this subset of AD which is associated with filaggrin deficiency there may be both a tendency to promote nickel allergy and *Staphylococcus* growth.\(^9\)

Of interest, FLG mutation carriers reported ACD to nickel at a significantly younger age than controls with normal filaggrin, and had stronger patch test reactivity.\(^9\) This positive association between FLG mutations and contact sensitivity (CS) to nickel has been reported in German adults and confirmed in Danish adults without ear piercings.\(^10\) The sources for the majority of the nickel sensitized (non-pierced) adult patients remains to elucidated.

That said, a number of studies have looked at sources associated with generalized dermatitis (SCD) in AD children. In one study, nickel release was evaluated from 212 children’s toys, which showed 34.4 percent of the toys released sufficient nickel to lead to sensitization or reactivation in a sensitized person.\(^11\) The majority of toys were gender neutral, however, a larger proportion of the gender-intended toys were directed at females.\(^11\) In a recent study by Goldenberg et al., 67 percent of the subjects demonstrated generalized dermatitis in association with a belt buckle, notably 75 percent had concurrent AD.\(^12\) It is important to note that nickel release from objects may be below the detectable level of the Dimethylglyoxime (DMG) test, as it is only 59.3 percent sensitive, which could lead to a false sense of reassurance.\(^13\) Furthermore, it stands to reason that the release of nickel onto a normal barrier versus one with filaggrin defects would confer a relative “greater dose” due to an increased absorption into the defective skin barrier.

**IMMUNE RESPONSE TO NICKEL IN STAPHYLOCOCCUS INFECTED AD PATIENTS:**

There are increasing reports of generalized dermatitis associated with nickel in AD children from a number of sources, including the aforementioned belt buckles and toys.\(^11,12\) The immunology of these interactions is actually quite complex. In a recent study by Akan et al, utilizing the SCORAD (scoring atopic dermatitis) score, the extent of eczema (including trunk involvement), the score of sleep loss, and the pruritus level demonstrated a significant association with nickel sulfate (NS) sensitization than those without any reaction (\(P = 0.002, P = 0.001, \& P = 0.002\), respectively).\(^14\) This has led to several authors recommending evaluation for NS sensitization for children with severe AD or larger extent of eczema.

Significant immunological alterations have been reported, in which there is a decrease in TH1 and TH2 subset genes with nickel associated AD responses, including increased TH17/IL-23, inconsistent upregulation in the levels of TH2 products and abnormal

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**TABLE 1: PRE-EMPTIVE ACIDIFICATION AND ANTI-MICROBIAL MEASURES**

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<th>PRE-EMPTIVE MEASURES</th>
<th>EXAMPLES</th>
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<td>Acid Cleansers/Acidification</td>
<td>• Mild, non-alkaline cleansers are preferred.</td>
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| Acidification soaks | • Add vinegar (white or apple cider) to tap water, goal pH around 4.5.  
| | • Soak for 15-20 minutes.  
| | • Do not rinse the vinegar water from the skin after bathing.  
| | • Follow with emollient application and/or prescribed topical medicaments. |
| Aseptic Protocol\(^18\) | • Create a bathing pool at home in the bathtub with tapwater and household bleach (for ½ full tub - add ¼ cup of bleach).  
| | • Soak for 15 minutes, then rinse.  
| | • Follow rinse step with emollient application and/or prescribed topical medicaments. |
| Antibiotics | • Topical antibiotics should be reserved for short-term use in secondary bacterial infection.  
| | • 87 percent of *S. aureus* is resistant to penicillin and amoxicillin.  
| | • Cloxacillin and cephalaxin are often used to treat *Staphylococcus* infection in AD patients.\(^17\) |
negative regulator levels compared with those seen in non-AD skin, occurring simultaneously. These baseline abnormalities impact allergic immune reactions through global attenuation and differential polarization in patients with AD. This skewing and subsequent hyporesponsiveness in skin from patients with a history of AD could explain the inconsistencies in the literature regarding rates of sensitization in AD versus non-AD patients.

In the situation of a significant flare of generalized dermatitis reaction during patch testing that corresponds to a negative patch test read, a low-nickel diet trial may be warranted. Improvement through implementation for a low nickel diet has been noted in some moderate-severe AD children with negative or equivocal nickel patch tests. These same patients have been seen to later demonstrate nickel reactivity once their generalized dermatitis abates (and they become a mild-moderate atopic responding to emollients and topical medicaments), despite the earlier patch test being negative (personal observation, SEJ). This supports the hypothesis by Correa de Rosa that the significant decreases in levels of TH1 products, some increases in levels of TH17 products, and inconsistent upregulation in levels of TH2 products and negative regulators could explain the overall hyporesponsiveness in skin from patients with background AD compared with those seen in non-AD skin states.

Of interest, Admani et al. noted that pre-emptive Staphylococcus skin colonization reduction measures, such as utilizing anti-Staphylococcus antibiotic treatments, and aseptic soak protocol three weeks before patch testing can result in more effective patch test readings (reduced flares and background dermatitis) in AD patients known to have a history of supercolonization. Furthermore, it has been shown that alkaline soaps may induce lesions of susceptible persons with atopic dermatitis and thus utilizing acid maintaining cleansers and skin acidification is paramount. (See Tables 1 and 2)

Of interest, a randomized control trial suggested that bleach baths showed drastic progression towards improvement for AD patients, compared to oral antibiotics, topical steroids, and antibiotic ointments. This demonstrates the importance of counteracting the bacterial colonization, as bleach baths have an overall beneficial effect, even though they increase the pH (alkalinize) of the skin. Thus, pairing bleach baths with acidification, restoring the pH to be more acidic, rather than alkaline (pH of atopic 6.1 versus 5.24 in normal controls), enhances the skin’s antimicrobial properties, disrupts biofilm formation and restores the integrity of the normal biome and epidermal function. Furthermore, Staphylococcus and other pathogenic bacteria that favor growth in neutral pH are further inhibited in an acidic milieu.

Lastly, researchers have shown elevated secretion of IL-2 under nickel sulfate stimulation in vitro, specifically in AD patients with nickel allergy infected by S. aureus. The enhancement of IL-2 by Staphylococcus may promote activation of the lymphocytes, as autocrine feedback action leads to cell proliferation. This process, known as clonal expansion, is critical in the afferent phase of contact sensitization, and suggests a supportive role between the expression of nickel contact allergy and S. aureus infection in AD patients.

The environmental impact of the Staphylococcus biofilm formation and interaction with metals, the genetic component of filaggrin and nickel, and the complex immune response to nickel in mild, moderate, and severe Staphylococcus infected AD patients remains to be fully elucidated. Acidification of the skin is necessary for antibacterial activity and barrier function. Therapeutic options specifically addressing pH aberrancy, in the era of antibiotic resistance, could potentially not only improve AD by inhibition of Staphylococcus and pathogenic microbes, but may also impact sensitization rates to nickel.

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el. Clinicians should be encouraged to evaluate patterns of NS sensitization in children with atopic dermatitis and consider the impact of *Staphylococcus* colonization.

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