Aluminum: The 2022 American Contact Dermatitis Society Allergen of the Year

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PRACTICE **POINTS**

- Aluminum is an allergen of significance relating to its use in vaccines, immunotherapies, and antiperspirants.
- There is a greater prevalence of aluminum contact allergy in children than in adults, affecting up to 5% of the pediatric patch-test population.
- The recommended patch test formulation is aluminum chloride hexahydrate 10% in petrolatum, with consideration of reducing the concentration to 2% in children younger than 8 years to avoid strong reactions.

Aluminum recently was selected as the 2022 Allergen of the Year by the American Contact Dermatitis Society. Aluminum contact allergy, which most often is related to its use as an adjuvant in select vaccines and allergen-specific immunotherapies, tends to present with pruritic subcutaneous nodules at the injection site. Allergy to aluminum-containing antiperspirants manifests as axillary vault dermatitis. In this article, we highlight the growing recognition of aluminum contact allergy, particularly in the pediatric population, focusing on distinct presentations of aluminum allergic contact dermatitis (ACD), unique sources of exposure, and nuances of patch testing to this metal.

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No time of the year is more exciting than the unveiling of the American Contact Dermatitis Society Allergen of the Year. Sometimes the selected allergen represents a completely novel cause of allergic contact dermatitis (ACD) with an unpronounceable chemical name. Not this time! The 2022 Allergen of the Year is likely to be lurking in your kitchen drawer at this very moment, as this year aluminum was chosen for this most prestigious honor.[1] But do not throw out your aluminum foil just yet—aluminum allergy tends to be confined to specific scenarios. In this article, we highlight the growing recognition of aluminum contact allergy, particularly in the pediatric population, focusing on distinct presentations of aluminum ACD, unique sources of exposure, and nuances of patch testing to this metal.

Aluminum Is All Around Us

As the third most common element in the Earth's crust, aluminum can be found quite literally everywhere.[1] However, aluminum rarely is found in its pure elemental form; instead, it reacts with other elements around it, most commonly oxygen, to form aluminum-containing compounds. Known for their stability and safety, aluminum and its salts are incorporated in myriad products ranging from electronic equipment to foods and their

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Ms. Novack reports no conflict of interest. Dr. Yu is an immediate past member of the Board of Directors and chair of the Interactive Media Committee of the American Contact Dermatitis Society. He also has served as a speaker for the National Eczema Association and has received a research grant from the Dermatology Foundation. Dr. Adler has served as a research investigator and/or consultant for AbbVie and Skin Research Institute, LLC. He also is a member of the Board of Directors and chair of the CAMP Strategic Planning and Industry Support Committee of the American Contact Dermatitis Society.

The views expressed in this article are those of the authors and do not represent the views of the American Contact Dermatitis Society.

The eTable can be found in the Appendix online at www.mdedge.com/dermatology.

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packaging, medications, cosmetics, orthopedic and dental implants, and even tattoos. Aluminum also is found in the air and water supply and may even be encountered in certain workplaces, such as aircraft and machine industries. As such, contact with aluminum is all but certain in modern life.

The use of aluminum in consumer products is widely accepted as safe by public health agencies in the United States.[2] Although there has been public concern that aluminum could be linked to development of breast cancer or Alzheimer disease, there is no clear evidence that these conditions are associated with routine aluminum exposure through ingestion or consumer products.[3-5]

Aluminum Contact Allergy

In part because of its ubiquity and in part because of the stability of aluminum-containing compounds, it was long thought that aluminum was nonallergenic. Contact allergy to elemental aluminum is rare; on the other hand, aluminum salts (the forms we are likely to encounter in daily life) are now recognized in the field of contact dermatitis as allergens of significance, particularly in the pediatric population.[1,6]

First reported as a possible occupational allergen in 1944,[7] aluminum allergy came to prominence in the 1990s in association with vaccines. Aluminum is included in some vaccines as an adjuvant that bolsters the immune response[8]; the eTable lists currently available aluminum-containing vaccines in the United States; of note, none of the COVID-19 vaccines approved in the United States or Europe contain aluminum.[11] Although the use of aluminum in vaccines is considered to be safe by the US Food and Drug Administration and Centers for Disease Control and Prevention,[12,13] a small number of children become sensitized to aluminum through vaccines and may develop persistent pruritic subcutaneous nodules (also known as vaccination granulomas) at the injection site; however, the incidence of this adverse effect was less than 1% in large studies including as many as 76,000 children, suggesting that it is relatively rare.[14,15] Upon patch testing, aluminum allergy has been detected in 77% to 95% of such cases.[14] There is wide variation in the onset of the nodules ranging from weeks to years following vaccination.[15] Due to pruritus, the examination may reveal accompanying excoriations, hyperpigmentation, and sometimes hypertrichosis at the injection site. Aluminum allergy related to vaccination also can manifest with widespread eruptions representing systemic contact dermatitis.[16]

Along with vaccines, the second major source of aluminum sensitization is allergen-specific immunotherapies administered by allergists/immunologists, many of which contain aluminum hydroxide.[17,18]

On the consumer product front, antiperspirants are the most common source of cutaneous exposure to aluminum. Aluminum complexes react with electrolytes in sweat to form plugs in eccrine ducts, thereby preventing sweat excretion.[6] Allergic contact dermatitis to these products presents with axillary-vault dermatitis. There also have been reports of ACD to aluminum in sunscreen and toothpaste, with the latter implicated in causing systemic ACD.[19,20]

Prevalence of Sensitization to Aluminum

There have been a few large-scale studies evaluating rates of sensitization to aluminum in general patch-test patient populations; additionally, because of the complexities of testing this metal, investigators have utilized differing formulations for patch testing. A recent Swedish study found that 0.9% of 5448 adults and 5.1% of 196 children showed positive reactions to aluminum chloride hexahydrate (ACH) 10% in petrolatum and/or aluminum lactate 12% in petrolatum.[21] Notably, there was a significant association between aluminum allergy and history of atopy for both adults (P=.0056) and children (P=.046), which remains to be further explored. A systematic review and meta-analysis found comparable rates of aluminum allergy in 0.4% of adults and 5.6% of children without vaccine granulomas who were tested.[22] With this evidence in mind, it has been recommended by contact dermatitis experts that aluminum be included in pediatric baseline patch test series and also investigated for potential inclusion in baseline series for adults.[1]

Differential Diagnosis of Aluminum ACD

The differential diagnosis for subcutaneous nodules following vaccination is broad and includes various forms of panniculitis, sarcoidosis, foreign body reactions, vascular malformations, infections, and malignancies.[23-25] The diagnosis may be obscured in cases with delayed onset. Biopsy is not mandatory to establish the diagnosis; although variable histopathologic findings have been reported, a common feature is histiocytes with abundant granular cytoplasm.[26] It may be possible to demonstrate the presence of aluminum particles in tissue using electron microscopy and X-ray microanalysis.

For those patients who present with axillary-vault dermatitis, the differential includes ACD to more common allergens in antiperspirants (eg, fragrance), as well as other axillary dermatoses including inverse psoriasis, erythrasma, Hailey-Hailey disease, and various forms of intertrigo. Dermatitis localized to the axillary rim suggests textile allergy.

Patch Testing to Aluminum

Due to its physicochemical properties, patch testing for aluminum allergy is complicated, and historically there has been a lack of consensus on the ideal test formulation.[1,27,28] At this time, it appears that the most sensitive formulation for patch testing to aluminum is ACH 10% in petrolatum.[1] Some contact dermatitis experts recommend that children younger than 8 years should be tested with ACH 2% in petrolatum to minimize the risk of extreme patch test reactions.[29,30] In some patients sensitized to

aluminum, the use of aluminum patch test chambers has been noted to produce false-positive reactions, taking the form of multiple ring-shaped reactions to the chambers themselves or reactions to certain allergens whose chemical properties cause corrosion of the aluminum within the chambers.[31-33] Therefore, when testing for suspected aluminum allergy, plastic chambers should be used; given the higher prevalence of aluminum allergy in children, some clinics routinely use plastic chambers for all pediatric patch testing.[34] Importantly, elemental aluminum, including empty aluminum test chambers or aluminum foil, alone is not sufficient for patch testing as it lacks sensitivity.[1] Additionally, nearly 20% of positive tests will be missed if a day 7 reading is not performed, making delayed reading a must in cases with high suspicion for aluminum allergy.[21]

Management of Aluminum Allergy

The development of pruritic subcutaneous nodules is uncomfortable for children and their guardians alike and may be associated with prolonged symptoms that negatively impact quality of life[35,36]; nonetheless, expert authorities have determined that the preventive benefits of childhood vaccination far outweigh any risk posed by the presence of aluminum in vaccines.[12,13,37] Because aluminum-free formulations may not be available for all vaccines, it is essential to educate patients and families who may be at risk for developing vaccine hesitancy or avoidance.[35,36,38] Given the hypothesis that epidermal dendritic cells mediate aluminum sensitization, it has been proposed that vaccine administration via deep intramuscular rather than subcutaneous injection may mitigate the risk, but more evidence is needed to support this approach.[39,40] The good news is that the nodules tend to fade with age, with a median time to resolution of 18 to 49 months.[14] In addition, patients may experience loss of sensitization to aluminum over time[41]; in one study, 77% of 241 children lost patch test reactivity when retested 5 to 9 years later.[42] The exact reason for this diminishment of reactivity is not well understood. Adjunctive treatments to relieve symptoms of vaccine granulomas include topical and intralesional corticosteroids and antihistamines.

For patients reacting to aluminum in antiperspirants, there are many aluminum-free formulations on the market as well as recipes for homemade antiperspirants.[6] On a case-by-case basis, patients may need to avoid aluminum-containing medications, permanent tattoos, and orthopedic or dental implants. To the best of our knowledge, there is no evidence suggesting a need to avoid aluminum in foods and their containers in routine daily life; although some patients report exacerbations of their symptoms associated with food-related aluminum exposures (eg, canned food, dried fruit) and improvement with dietary modification, further investigation is needed to confirm the relevance of these sources of contact.[36,38] For patients who require allergen-specific immunotherapy, aluminum-free allergen extracts are available.[6]

Final Interpretation

Exposure to aluminum is ubiquitous; although relatively uncommon, awareness of the potential for ACD to aluminum is increasingly important, particularly in children. Given the prevalence of aluminum contact allergy, it has been recommended by contact dermatitis experts for inclusion in baseline pediatric patch test series.[1] Although it is a complex issue, the development of ACD in a small proportion of children exposed to aluminum in vaccines does not outweigh the benefit of vaccination for almost all children. When conducting patch testing to aluminum, studies support testing to ACH 10% in petrolatum for adults, and consider reducing the concentration to ACH 2% for children.

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APPENDIX

eTABLE. Vaccines Containing Aluminum Adjuvants Currently Available in the United States[9,10]

Vaccine	Trade name(s)(company)
Anthrax Vaccine Adsorbed	BioThrax (Emergent BioSolutions)
Diphtheria and Tetanus Toxoids Adsorbed	None
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed	Daptacel (Sanofi Pasteur Limited), Infanrix (GlaxoSmithKline)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined	Pediarix (GlaxoSmithKline)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine	Kinrix (GlaxoSmithKline), Quadracel (Sanofi Pasteur Ltd)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate and Hepatitis B Vaccine	Vaxelis (MSP Vaccine Company)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus B Conjugate (Tetanus Toxoid Conjugate) Vaccine	Pentacel (Sanofi Pasteur Ltd)
Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate) (Liquid)	PedvaxHIB (Merck & Co, Inc)
Hepatitis A Vaccine, Inactivated	Havrix (GlaxoSmithKline), Vaqta (Merck & Co, Inc)
Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine	Twinrix (GlaxoSmithKline)
Hepatitis B Vaccine (Recombinant)	Engerix-B (GlaxoSmithKline), PreHevbrio (VBI Vaccines Inc), Recombivax HB (Merck & Co, Inc)
Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant	Gardasil (Merck & Co, Inc)
Human Papillomavirus 9-valent Vaccine, Recombinant	Gardasil 9 (Merck & Co, Inc)
Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant	Cervarix (GlaxoSmithKline)
Japanese Encephalitis Virus Vaccine, Inactivated, Adsorbed	Ixiaro (Valneva)
Meningococcal Group B Vaccine	Bexsero (GlaxoSmithKline), Trumenba (Pfizer Inc)
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)	Prevnar 13 (Pfizer Inc)
Pneumococcal 15-valent Conjugate Vaccine	Vaxneuvance (Merck & Co, Inc)
Pneumococcal 20-valent Conjugate Vaccine	Prevnar 20 (Pfizer Inc)
Tetanus and Diphtheria Toxoids, Adsorbed	TdVax (Grifols)
Tetanus & Diphtheria Toxoids Adsorbed for Adult Use	Tenivac (Sanofi Pasteur Ltd)
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Adacel (Sanofi Pasteur Ltd), Boostrix (GlaxoSmithKline)
Tick-borne Encephalitis Vaccine	TicoVac (Pfizer Inc)