

ALLERGEN Focus



Focus on T.R.U.E. Test Allergens #23: Thimerosal

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Allergic contact dermatitis (ACD) is an important disease with high impact both in terms of patient morbidity and economics. The contact dermatitides include allergic contact dermatitis, irritant contact dermatitis and contact urticaria.

Irritant contact dermatitis, the most common form, accounts for approximately 80% of environmental- and occupational-based dermatoses.

Contact urticaria (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis; the foremost example of this would be latex hypersensitivity. Although

this is beyond the scope of this section, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key sources.^{1,2}

Allergic contact dermatitis represents a T helper cell Type 1 (Th1) dependent delayed-type (Type IV) hypersensitivity reaction.

The instigating exogenous antigens are primarily small lipophilic chemicals (haptens) with a molecular weight less than 500 Da.

Unlike other haptens, metal antigens do not covalently bind to carrier proteins; instead they complex with proteins similar to the binding of cobalt and vitamin B₁₂.¹

On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated that includes cytokines, i.e. interleukin 2 (IL-2) and interferon gamma (IFN- γ), T cells and Langerhan cells. This complex interaction leads to the clinical picture of ACD, an important disease with high impact both in terms of patient morbidity and economics.

The primary focus of this section is to highlight the educational component of allergic contact dermatitis.

CLINICAL ILLUSTRATION

A woman presented to the University of Miami Contact Dermatitis Clinic with a 6-year history of generalized pruritus and inflammation of her eyelids treated unsuccessfully with antihistamines and topical corticosteroids.

Of note, she also had a small tattoo with a papular reaction in the area of red pigmentation. She did not know the ink constituents.

THE HISTORY OF THIMEROSAL

Thimerosal, C₉H₉HgNaO₂S, is a mercuric derivative of thiosalicylic acid that goes by many names (*see Table 1*). It has been used as a disinfectant (Merthiolate) and a preservative in some vaccines, cosmetics, tattoo inks, eye drops and contact lens solutions.

The FDA banned the sale of topically applied thimerosal antibiotics in the 1980s due to severe, even crippling, adverse skin reactions in sensitive individuals. And, in July 1999, the U.S.

TABLE 1

COMMON SYNONYMS OF THIMEROSAL

- Ethyl (2-mercaptobenzoato-S) mercury sodium salt
- Mercurochrome
- Mercurothiolate
- Merfamin
- Merthiolate
- Mertorgan
- Merzonin
- Sodium ethylmercurithiosalicylate
- Thiomersal
- Thiomersalan
- Thiomersalate
- [(o-carboxyphenyl)thio] Ethylmercury sodium salt

Department of Health mandated the reduction of thimerosal in routine pediatric vaccines.

In 2004, California and Iowa passed bans of mercury in all vaccinations, and seven other states have similar legislation in progress.³

The main concern with thimerosal involves its metabolite — ethyl mercury. Hat makers, or “hatters” in the 1800s were notorious for suffering from dementias due to the mercury nitrate used in felt processing. This mercury-associated dementia in felt workers was the inspiration for the Mad Hatter in Lewis Carroll’s *Alice in Wonderland* and the origin of the phrase “mad as a hatter”. The Mad Hatter’s disease, also known as erythrism, includes a constellation of dementia, stomatitis, muscle spasm, tremor and skin rashes.⁴

The ethyl mercury from thimerosal is chemically similar to methyl mercury, which is 5 to 20 times as toxic as inorganic mercury in its effects on the human central nervous and endocrine systems.

Acute or chronic exposure to organic and inorganic mercury can result in renal, neurologic and dermal toxicity.

Neurologic and psychiatric sequelae include tremor, muscle weakness, peripheral neuropathy, metallic taste, hypersalivation, memory loss, erythrism, depression, anxiety and psy-

chosis. Because of the major neurological risk mercury poses to the unborn fetus, pregnant women are cautioned to limit the consumption of high mercury-containing fish to just once a month.

Cutaneous changes may include contact dermatitis, burning of the face, grey or blue-black facial discoloration, flushing, erythroderma, purpura and gingivostomatitis.⁵

MERCURY IN THE ENVIRONMENT

Mercury pollution in the environment has increased threefold since the industrial revolution, with soil deposition rates ranging from 5 to 15 µg/m²/year.⁶

The major sources of environmental mercury are coal-fired power plants, metal smelting, gold production, and

ported “Lewis and Clark latrines” around the country have uncovered the locations of their campsites.⁷

Mercury is a bioaccumulative toxin that is readily absorbed through the skin, respiratory and gastrointestinal systems.⁸ Methyl mercury in the environment works its way up the food chain in fish through bioaccumulation, reaching especially high levels in larger species such as shark (0.99 parts per million, or ppm), swordfish (0.97 ppm), and tuna (0.38 ppm).

FDA toxicologists recommend limiting the consumption of shark and swordfish to 7 ounces (one serving) a week, and the consumption of fresh tuna to 14 ounces a week (canned tuna has around half the methyl mercury content of fresh tuna). Other animals that may accumulate mercury include sea birds (that feed on mercury contaminated fish).

The U.S. Environmental Protection Agency (EPA) limit for mercury content in tap water is 2 parts per billion (ppb), while the limit for cosmetics is 65 ppm (21CFR700.13). The average daily mercury exposure from tap water and air in the general population is a thousand-fold less than that from seafood intake.⁹

No correlations have been published regarding mercury content in tap water and allergic contact dermatitis.

HOTLY DEBATED LINK

Just how similar the effects of ethyl mercury (from thimerosal) and methyl mercury are on the human body is the subject of much debate, with research suggesting that ethyl mercury stays in the body for a shorter period of time and is generally less harmful.

Research is underway at the National Institutes of Health to determine the safety guidelines for thimerosal in the hotly debated questionable link between thimerosal and the development of childhood neurological problems, such as autism.¹⁰⁻¹³

While most patients do not experience an immediate allergic reaction to thimerosal-containing intramuscular vaccines, the potential remains for delayed hypersensitivity and toxic systemic effects.

THE LEWIS AND CLARK
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AILMENTS.

the disposal (storing in landfills, incinerating) of mercury containing products such as batteries, fluorescent bulbs and thermometers.

Of historical interest, the persistence of mercury in the soil allowed archeologists studying the Lewis and Clark expedition insight into the trail route. During their travels, the Lewis and Clark pioneers were known to ingest “Thunderclappers” (pills nearly 60% concentrated mercury) for gastrointestinal ailments. Traces of mercury in pur-

TABLE 2

PRODUCTS CONTAINING THIMEROSAL/MERCURY

ANTIBIOTICS FOR THE EYE	Cortisporin Ophthalmic Suspension; Neosporin Ophthalmic Solution
CONTACT LENS SOLUTION	Bausch & Lomb Sterile Preserved Saline Solution, Allergan Hydrocare, Advanced Medical Optics LC-65, Ocufen
TOPICAL MEDICATIONS, ANTI-FUNGALS, ANTISEPTIC SPRAYS	Mercurochrome (banned in the United States, but used in other countries as antiseptic), Merchromine
HORMONE INJECTIONS	Testaqua, Testamone
NASAL PREPARATIONS	Nasal Moist AF; Neo-Syneprine Pediatric Formula, Mild Formula, Regular Strength, and Extra Strength Nasal Spray
EAR PREPARATIONS	Coly-mycin S Otic; Cortisporin Otic Suspension; Pediotic Suspension
COSMETICS, BLEACHING CREAMS	L'Oreal Miracle Wear Mascara, Stagelight Mascara, Miss Key Whitening Cream, Crema Santa, Dermaline Cream, Crema de Belleza (all banned in the United States, but still being sold) ²¹
VACCINES	Engerix-B, FluShield and Fluzone, Hep-B-Gammagee, HyperHEP, HyperTET Tetanus and diphtheria toxoids, Menactra, Menomune, Recombivax HB
TATTOO INK	Cinnabar (mercuric sulfide)

THIMEROSAL USE IN PRODUCTS

In addition to vaccines and antitoxins, thimerosal is also used as a preservative in cosmetics, such as makeup removers, eye moisturizers, mascaras and bleaching creams¹⁴ (see Table 2).

It is found in soap-free cleansers, nose/eye/eardrops, topical medications, anti-fungals, antiseptic sprays, contact lens solutions, hormonal injections and tattoo inks.⁸

Tosti et al. reported patients who had follicular allergic contact conjunctivitis induced by thimerosal-containing eye drops.¹⁵

WHO IS AFFECTED?

Demographically, thimerosal allergy is more commonly found among women, healthcare workers and cooks.

The increased incidence of thimerosal allergy in women may be explained by the presence of the compound in certain eye cosmetics.

The increased incidence in cooks and healthcare workers is related to the increased prevalence of vaccinations associated with these professions.

In addition, people allergic to thimerosal are more likely to be allergic to neomycin, bacitracin and tixocortol pivalate, due to the fact that these aller-

gens are often used in combination with one another in products and co-sensitization occurs.¹⁶

Thimerosal-sensitive patients can either be allergic to the mercuric moiety (most common) or the thiosalicylic acid moiety (these patients are advised to avoid piroxicam, which also contains this moiety).^{17,18}

Cinnabar (mercuric sulfide) used in red tattoo inks can lead to allergic reactions and scarring. Tsuruta et al. reported a case of a 40-year-old Japanese man with a red tattoo who developed a whole-body rash after eating 250 g of raw swordfish and alfonso.¹⁹ In this case the mercuric tattoo pigments caused the initial sensitization to mercury in the patient, producing a delayed hypersensitivity reaction.

Subsequent exposure of the patient to mercury-containing products either through ingestion/inhalation/injection (mercury vapor, mercury-laden fish, vaccines, toxoids, amalgam dental fillings) or direct contact (mercury-containing creams, contact lens solution) precipitated the allergic contact dermatitis.

While the ink compositions that are used in tattoos and permanent makeup are *subject* to FDA regulation, this has not been enforced. Importantly, no ink is approved for injection into the skin, which is what entails the actual practice of tattooing.²⁰ Further compounding the difficulty in regulation is that manufacturers of inks and pigments are not required to reveal the contents, since the information is proprietary. Inks vary

TABLE 3

QUESTIONS TO ELICIT MERCURY EXPOSURE RISK

DOES/DID THE PATIENT:

- work in the chemistry industry or a laboratory?
- have mercury fillings (dental amalgam) or work in a dentist's office?
- have a mercury thermometer at home or any recent accidents involving mercury thermometers?
- wear contacts (contact lens solution)?
- have any meals containing swordfish/alfonso/fresh tuna/shark associated with the breakout?
- use any cosmetic products containing thimerosal/mercury?
- recently have a vaccination or tetanus shot?

by manufacturer, even among like-colored pigments.

With the recent growth in popularity of tattoos, the FDA is taking a closer look at related safety questions regarding adverse reactions to tattoo colors.²¹

TESTING FOR THIMEROSAL SENSITIVITY

Patch testing for thimerosal allergy can be accomplished with the thin-layer rapid-use epicutaneous (T.R.U.E.) test (site #23).

The T.R.U.E. test is the commercially available, globally used, allergen screening system. While it is widely used, the discrepancy in allergen prevalence and uncertain relevance has led to scrutiny of its utility. The T.R.U.E. test contains 23 allergens and one negative control. At best, this test is a minimum screening tool, as it tests only 23 of the more than 3,700 possible allergens that can cause allergic contact dermatitis.

Krob et al. recently demonstrated through meta-analytic techniques that nickel, thimerosal, cobalt, fragrance and balsam of Peru are the most prevalent allergens detected by the T.R.U.E. test. They noted that a significant number of relevant allergens, not present on the T.R.U.E. test, would potentially be missed by this screening tool alone.²¹

THE VALUE OF THIS PATIENT CASE

Our patient tested positive for thimerosal. The patient deferred surgical excision of her red tattoo. Thus, we treated the papular reaction in the tattoo with topical corticosteroids and implemented a strict avoidance regimen, including substitution of mercury-free personal products and a low mercury diet. Notably, her eyelid edema and pruritus dramatically improved.

Once an allergen is identified, patient education on allergen **avoidance** is of the utmost importance, as the mainstay of treatment for allergic contact dermatitis is lowering the exposure dose to the allergen. The first step in avoidance is the knowledge of what not to use.

This patient underscores the importance of appropriate allergen patch testing, the need for education and regulation of mercurial pigments used in tat-

too art, and the potential for systematized contact dermatitis in individuals with red tattoos. ■

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WITH THE RECENT GROWTH IN POPULARITY OF TATTOOS, THE FDA HAS BEGUN TAKING A CLOSER LOOK AT RELATED SAFETY QUESTIONS REGARDING ADVERSE REACTIONS TO TATTOO COLORS.

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