Metal Hypersensitivity Dermatitis

Peter C. Schalock, MD
Disclosures

• I have no relevant commercial interests or relationships to disclose
• Common reactions to metals
• Metal Hypersensitivity Reactions (MHR) to implanted devices
• Evaluation of MHR
• Distant reactions to systemic metal exposures
Metal Mania
Epidemiology

• Metal allergy is common
  – NACDG 2017-18: 16.2% Ni, Co 6.7%, Cr 1.6% (Dekoven 2021)
    • Ni: ~19% of adult women; 3% of adult men (Thyssen et al. 2007)(Warshaw 2015)
    • Au: ~23% of both genders (Tam, 2020 in press)

  – Prevalence of other metals, e.g. titanium, platinum, molybdenum, manganese, vanadium
    • Generally infrequent in dermatitis patients
    • Few large studies examining patch test results for less common metals
### TABLE 4. Comparison of Metal Sensitivity Prevalence by Sex and Age

<table>
<thead>
<tr>
<th>Allergen*</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel sulfate hexahydrate 2.5 pet</td>
<td>26.2</td>
<td>33.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Gold sodium thiosulfate 0.5 pet</td>
<td>23.0</td>
<td>26.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Gold sodium thiosulfate 2.0 pet</td>
<td>20.7</td>
<td>25.9</td>
<td>7.1</td>
</tr>
<tr>
<td>Palladium chloride 2.0 pet</td>
<td>19.6</td>
<td>25.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Cobalt (II) chloride hexahydrate 1.0 pet</td>
<td>12.0</td>
<td>14.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Manganese (II) chloride 2.0 pet</td>
<td>10.1</td>
<td>10.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Vanadium 5.0 pet</td>
<td>7.5</td>
<td>7.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Potassium dichromate 0.1 aq</td>
<td>6.8</td>
<td>8.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Potassium dichromate 0.25 pet</td>
<td>6.5</td>
<td>7.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Copper sulfate 2.0 pet</td>
<td>6.0</td>
<td>6.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Stannous chloride 1.0 pet</td>
<td>5.4</td>
<td>6.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Mercury 0.5 pet</td>
<td>3.4</td>
<td>4.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Mercury ammonium chloride 1.0 pet</td>
<td>2.7</td>
<td>3.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Vanadium (III) chloride 1.0 pet</td>
<td>2.7</td>
<td>3.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Mercuric chloride 0.1 pet</td>
<td>2.7</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Iridium (III) chloride trihydrate 10.0 aq</td>
<td>2.7</td>
<td>2.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Iron (III) chloride 2.0 pet</td>
<td>2.7</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Zirconium chloride 1.0 pet</td>
<td>2.0</td>
<td>2.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Zinc chloride 2.0 pet</td>
<td>2.0</td>
<td>0.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Iridium 1.0 pet</td>
<td>1.4</td>
<td>1.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Indium 1.0 pet</td>
<td>1.4</td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Calcium titanate 10.0 pet</td>
<td>0.7</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Copper (I) oxide 5.0 pet</td>
<td>0.7</td>
<td>0.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Zinc 2.5 pet</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lead acetate trihydrate 0.5 aq</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Molybdenum 5.0 pet</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Stannous oxalate 1.0 pet</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cadmium chloride 1.0 aq</td>
<td>0.7</td>
<td>0.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Titanium oxalate 5.0 pet</td>
<td>0.7</td>
<td>0.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Titanium oxide 10.0 pet</td>
<td>0.7</td>
<td>0.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

*Allergens are presented as their respective metal salts or compounds.
Cutaneous ACD to metals

- Stainless Steel
  - Ni, Co, Cr, V, Mb
- Gold
  - Skin
  - Mucosal
- Ni, Co, Cr, Au on many standard series
Nickel sulfate

• One of the most common allergens (all ages)
  – Adults 16-18%
  – Children 13 – 28% (Bruckner)(Zug)

  – Jewelry/Everyday products
  – Orthopedic implants & Endovascular devices
  – Oral Ingestion
  – Medical devices
Cobalt II chloride hexahydrate

• Co-reacts with Nickel (Brandão, 2012)

• Many orthopedic devices are cobalt-chromium-molybdenum (Ni ~1%)
Potassium Dichromate

- Leather
- Cement industry
- Tattoos

- Orthopedic joint systems
  - especially cobalt-chrome alloys
Nitinol

- Nickel-Titanium systems = Nitinol
  - 55% Nickel / 45% Titanium
  - Superelastic/Temp dependent
  - Stents, Gynecological Devices

https://en.wikipedia.org/wiki/Nickel_titanium
Biomedical Devices

• Primarily composed of metal alloys, plastic components, Silicone
  – Stainless Steel
    • 316L (~16% Ni)
    • CoCrMo (~1% Ni)
  – Nitinol (55% nickel/45% titanium)
  – Oxidized Zirconium
  – Titanium
    • Ti6Al4V/TiNbN
    • Trace Ni
Review Article
Biomaterial Hypersensitivity: Is It Real?

• Does it make a difference for our patients?

• Do we care about potential MHR?
CASES

Is MHR to implanted devices real?
52 y/o woman

- Metal reactions “since childhood”
- Causes itchy, blisters and redness with “any metal exposure” on the skin snaps/ear rings and really anything metal bothers
- TMT joint fusion for hallux valgus and arthritis on right foot March 5, 2012
  - Within 24 hours with itching/redness and blistering started on dorsal foot around the incision site
- Surgical wounds – 6 months to close
- Fatigue and "tin can" taste in mouth since the surgery
- Patch test +: Nickel, Chromium, Bacitracin

**Past skin history:**
No personal or family history of psoriasis.

**Atopic history:**
  - Asthma -
  - Seasonal Allergies -
  - Atopic Dermatitis -
MOST FREQUENT COMPLICATIONS OF METAL IMPLANT HYPERSENSITIVITY
MHR is uncommon

• Orthopedic devices
  – Old MoM -> definitely happened
  – Newer MoP -> much rarer reactions
**Cutaneous allergic complications orthopaedic implants**

- Reports starting in the 1960’s
  - localized allergic dermatitis
  - urticaria
  - impaired wound healing overlying the metallic implant
  - systemic allergic dermatitis reactions distant anatomical sites
  - cutaneous vasculitis
Extra-cutaneous allergic complications orthopaedic implants

• **Pseudotumor/Metallosis**
  – Delayed type hypersensitivity reactions (Hallab & Jacobs 2009)
    • Solid or cystic masses communicate with the prosthesis
    • Cell and tissue necrosis/heavy macrophage response to wear particles and are often accompanied by an ALVAL infiltrate
  – Metal ions activate, **adaptive type IV response** (Hallab 2008)
  – Large particulate wear debris phagocytosed by macrophages

• **ALVAL** (aseptic lymphocyte-dominated vasculitis-associated lesion)
  – Perivascular lymphocytic/plasma cell infiltrate
    • Found in peri-prosthetic tissues in response to the deposition of cobalt-chromium wear particles
  – Immune reactions INCLUDE Type IV reactions (multifactorial)
• Aseptic Loosening
  – implant debris recruits macrophages/osteoclasts to peri-prosthetic regions = **bone resorption**

• Cutaneous Reactions
  – Bx often c/w type IV hypersensitivity
# ACD from Bone Cement Components

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Use</th>
<th>~% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>N,N,-dimethyl-p-toluidine</td>
<td>Reaction initiator</td>
<td>10</td>
</tr>
<tr>
<td>Polymethyl methacrylate (MMA)</td>
<td>Cement base</td>
<td>25</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
<td>Activator</td>
<td>8-10</td>
</tr>
<tr>
<td>Hydroquinone</td>
<td>MMA stabilization</td>
<td>5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Antibiotic</td>
<td>17-24</td>
</tr>
</tbody>
</table>
Cardiac Stents

• Materials used in US:
  – 316L stainless steel (Ni 12%, Cr17%, Mb2%)
    • Gold plated stents – use discontinued due to clear ISR risk (Svedman, 2009)
  – Cobalt-chromium alloys (Ni 9-35%)
  – Platinum-cobalt alloys (Ni 9%)
  – Nitinol (55% nickel, 45% Titanium)

• Drug Eluting stents
  – ISR rates decreased initially, ISR increases again after the immunosuppressive coating diminishes
MHR to Vascular/Cardiac Implants

- Gong, 2013
  - Increased risk of ISR with metal allergy
  
  - Meta-analysis 2013: 9 studies, 1,223 patients
    - Pre-existing metal allergy pose an increased risk of ISR, with an odds ratio of 2.65
  
  - OR for Asian patients were higher than European patients (3.71 vs 2.25)
    - Former group may be more susceptible to ISR

In-stent Restenosis

• Retrospective studies – nickel implicated in ISR of bare metal stents
• Prospective studies – No confirmed association
• Drug eluting stents
  – Case series – late ISR in metal allergic patients
• Recurrent restenosis patients
  – 2 studies: higher rates of ISR in Ni allergic patients
Kounis syndrome

– Acute ISR secondary to hypersensitivity to stent components (Nickel)
  • Involves release of inflammatory cytokines through mast cell activation, which leads to coronary artery vasospasm and/or atheromatous plaque erosion or rupture

– Tangent → Nickel exposure elicits type I reactions (acute and chronic urticaria)

# Role of contact sensitization in chronic urticaria

Laura Guerra, MD, Anthi Rogkakou, MD, Piera Massacane, MD, Cinzia Gamalero, BS, Enrico Compalati, MD, Cristian Zanella, MD, Antonio Scordamaglia, MD, Walter G. Canonica, MD, and Giovanni Passalacqua, MD

*Genoa, Italy*

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**Table II. Patch test results**

<table>
<thead>
<tr>
<th>Compound</th>
<th>No. of patients testing positive</th>
<th>M/F (No.)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metals</td>
<td>20</td>
<td>5/15</td>
<td>13 nickel, 6 cobalt + nickel 1 cobalt</td>
</tr>
<tr>
<td>Chemical</td>
<td>16</td>
<td>7/9</td>
<td>6 parabens, 3 colophony, 2 benzocaine, 1 thiram mix, 1 bisulfites, 1 potassium dichromate</td>
</tr>
<tr>
<td>Cleaning agents/cosmetics</td>
<td>9</td>
<td>3/6</td>
<td>6 balsam of Peru, 1 fragrances mix 1 Kathon, 1 thimerosal</td>
</tr>
<tr>
<td>Stabilizers/accelerators</td>
<td>5</td>
<td>1/4</td>
<td>3 ethylenediamine 2 mercaptobenzothiazole</td>
</tr>
</tbody>
</table>
Other intravascular devices

• Amplatzer Devices (NiTi) for VSD closure
  – Arrhythmias
  – Systemic Dermatitis
  – Chronic Migraine headaches

• Other stent devices
MHR to other implants

• Pacemakers & Spinal cord stimulators
  – Titanium, polyurethanes, silicone rubber, silicone adhesive -> External exposures
  – Alternative coatings
    • Parylene
    • Gold

• Stainless steel sternal wires

• Nuss Procedure
  – Patch testing prior recommended for all patients
Approaches to MHR
Who should get tested?

• Two common scenarios
  – *Pre-implantation*
  – *Post-implantation*
Delphi analysis (N=18)

- **See no evil (Ignore the data)**
  - “Most respondents agreed in proceeding with cobalt chromium or stainless steel implant in patients suspected of metal allergy regardless of the results of cutaneous patch testing”

- **Hear no evil (Don’t ask)**
  - “Patients having metal arthroplasty surgery should not be routinely questioned about metal allergy prior to surgery”

- **Speak no evil (Don’t tell)**
  - “Patch testing is not necessary even if metal allergy is suspected”
Who should be tested prior to implant?

- European Perspective: Nobody needs testing:
  - UK: “standard cobalt chromium/stainless steel implants should be used regardless of the patient’s metal allergy status” Bruze, 2008
  - Sweden: “virtually no such patients are evaluated” Bruze, 2008
  - Germany: if metal allergy suspected, use titanium alloys Thomas, 2008
  - Denmark: h/o “clinical metal intolerance of a magnitude sufficient to cause concern to the patient or the doctor” Thyssen, 2011

- United States
  - ACDS: Schalock, 2016
    - Pre-implantation:
      - “Routine preoperative evaluation in individuals with no history of metals reaction or history of previous implant-related adverse events is not necessary.”
      - “Patients with a clear self-reported history of metal reactions should be evaluated by patch testing before device implant”
    - Post-implantation testing:
      - Patients with chronic unexplained issues such as implant loosening or failure.
Assessing the validity of self-reported history of rash caused by metal or jewellery

• 10 years, MGH Contact Clinic; N=2,132

• “Do you get rashes when your skin is exposed to jewelry?”
  – 40% sensitive
  – PPV 51%, NPV 82%

• “Do you have rashes when your skin is exposed to metal?”
  – 77% sensitive
  – PPV 71%, NPV 84%

  – Q2 was both 37% more sensitive than Q1 (p<0.0001), with a higher relative risk (4.75, p<0.001) compared to Q1 (RR=3.01, p<0.001)
Patient is referred prior to surgery for evaluation

• No routine screening is indicated unless significant concern exists (surgeon or patient)

• Do they have a history of cutaneous metal reactions?
  – Yes? Yes.
  – No? No testing is indicated unless significant concern exists (surgeon or patient)

• Prior to implantation of Nuss bar placement
  – Test everyone
Who should get tested?

• Two common scenarios
  – *Pre-implantation*
  – *Post-implantation*
Patient is referred after surgery with symptoms

- History of metal reaction?
- Dermatitis above or adjacent to the implant?
- Widespread/generalized dermatitis following implant placement?
- Histopathology c/w hypersensitivity reaction?

- Consider patch testing for these individuals
- Post-implant MHR -> Diagnosis of exclusion
What test is best?

• Patch test vs. Lymphocyte transformation test
  – Or both (?)

• What do you test for?
  – Let the testing fit the question

• NO test is clearly predictive of implant reactions
SYSTEMIC HYPERSENSITIVITY TO CHRONIC METAL EXPOSURE
Other Medical Devices

• Orthodontic devices
  – Usually local reactions, but regional/systemic ACD possible

• Gynecological device - Essure
Essure

• Permanent contraceptive implants

• Outpatient placement

Essure Contraceptive

• Components
  – Inner coil: Stainless steel
  – Outer coil: Nitinol
  – Central core: polyethylene (PET) fibers (Dacron)
  – Expands in the Fallopian Tubes

• Taken off the market by Bayer in 2018

http://www.essuremd.com/LinkClick.aspx?link=Skins%2fConceptus_Skin%2fPDFs%2fCC-0533-safety-effectiveness.pdf&tabid=66
Systemic Nickel Allergy Syndrome (SNAS)

- Systemic nickel exposure causes **systemic** issues, not just a cutaneous contact dermatitis.
- Currently, SNAS includes those with:
  - positive nickel skin test that have symptoms flare with **gastrointestinal** nickel exposure
  - ~1-5% of all individuals who are nickel hypersensitive have a SNAS-like reaction
Systemic Hypersensitivity to Chronic Metal Exposure

• Systemic Nickel Allergy Syndrome (SNAS)
  – *Skin*: Urticaria, “rashes”, AD flares, pompholyx or “hand dermatitis”, alopecia
  – *Respiratory*: Asthma flares, rhinitis
  – *Gastrointestinal*: Intestinal inflammation leading to abdominal bloating and gastric pain, diarrhea or constipation, vomiting and nausea
  – *Systemic*: Headaches, chronic fatigue, fever, arthralgias.

Should the concept of SNAS be expanded?

Hypothesis only...

• Does systemic nickel/metal exposure (Non-GI) cause a SNAS-like reaction in a minority of patients?
Metal hypersensitivity may contribute to autoimmunity?

- Metal-specific T cell reactivity may cause the development and chronification of rheumatic disease (SLE/RA/SS) [Bjørklund]
  - increased frequency of metal delayed-type hypersensitivity, to nickel, titanium as well as other metals

- Reported autoimmunity (ASIA) from a nitinol device [Loyo]

- Nickel chloride exposure by an oral or subcutaneous route inducted autoimmunity and systemic sclerosis in rats. [Al-Mogairen]
  - Prolonged exposures increased the risk of developing autoimmunity

Nickel allergy and other autoimmunity

- **Autoimmune thyroiditis** may develop at a significantly higher rate in individuals with nickel allergy and especially a history of systemic nickel allergy syndrome (SNAS) [Andrioli, 2015] [Wesner, 2019]

- **Fibromyalgia** and **Chronic Fatigue Syndrome** are associated with delayed-type hypersensitivity to metals, especially nickel [Stejskal, 1999] [Stejskal, 2014] [Bjørklund, 2018]

- **Systemic Lupus Erythematosus, Rheumatoid Arthritis** and **Systemic Sclerosis** patients have increased frequency of metal delayed-type hypersensitivity compared to control populations.
  
  - Metal-specific T cell reactivity may be the cause of development and chronification of rheumatologic disease [Bjørklund, 2018]
<table>
<thead>
<tr>
<th>My Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IV reaction to implanted devices is a real, but rare problem</td>
</tr>
<tr>
<td>Ignoring a patient’s concern about allergy isn’t a good choice</td>
</tr>
<tr>
<td>If possible, the most functional device with lowest allergen % should be chosen</td>
</tr>
<tr>
<td>In some cases, systemic type IV reactions may drive systemic symptoms (i.e. non-dermatologic)</td>
</tr>
</tbody>
</table>
Bored yet?
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