Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use

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Summary

Cutaneous and systemic hypersensitivity reactions to implanted metals are challenging to evaluate and treat. Although they are uncommon, they do exist, and require appropriate and complete evaluation. This review summarizes the evidence regarding evaluation tools, especially patch and lymphocyte transformation tests, for hypersensitivity reactions to implanted metal devices. Patch test evaluation is the gold standard for metal hypersensitivity, although the results may be subjective. Regarding pre-implant testing, those patients with a reported history of metal dermatitis should be evaluated by patch testing. Those without a history of dermatitis should not be tested unless considerable concern exists. Regarding post-implant testing, a subset of patients with metal hypersensitivity may develop cutaneous or systemic reactions to implanted metals following implant. For symptomatic patients, a diagnostic algorithm to guide the selection of screening allergen series for patch testing is provided. At a minimum, an extended baseline screening series and metal screening is necessary. Static and dynamic orthopaedic implants, intravascular stent devices, implanted defibrillators and dental and gynaecological devices are considered. Basic management suggestions are provided. Our goal is to provide a comprehensive reference for use by those evaluating suspected cutaneous and systemic metal hypersensitivity reactions.

Key words: allergic contact dermatitis; implant reactions; metals; patch tests.

Cutaneous and systemic hypersensitivity reactions to implanted metals are challenging to evaluate and treat. The incidence and prevalence of such hypersensitivity reactions are unknown, as the literature lacks longitudinal prospective trials with clear objective criteria and large cross-sectional studies. In the past, it was considered that only a few (<1%) individuals would develop cutaneous complications from implanted metals. This might be an underestimate, as a recent case series showed that up to 5% had metal-related cutaneous complications post-implant (1). Whether they are performing patch testing or not, physicians may be asked for clinical advice regarding metal hypersensitivity. This may occur either prior to implantation or after surgery, when delayed-type hypersensitivity reactions are suspected. Thus, dermatologists should continuously keep updated about this difficult area of contact allergy of growing importance (2).

The association between metal allergy and implant failure was reviewed recently (3), and an in-depth review focusing on the association between metal allergy and cardiac devices was performed in 2008 by Honari

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et al. (4). Another review suggested a pragmatic approach to the diagnostic work-up of patients suspected of having implant-related metal allergies and complications (5). Here, we attempt to take the clinical work-up of implanted patients one step further by identifying the metal-related and device-related allergens contained in frequently used static and dynamic orthopaedic implants, intravascular stent devices, and dental and gynaecological devices. Furthermore, we suggest a diagnostic algorithm and an appropriate screening allergen series for patch testing. Our goal is to provide a concise, comprehensive reference for use by those evaluating suspected cutaneous and systemic metal hypersensitivity reactions that will hopefully lead to more quantitative biologically based evaluations.

Metal Allergy and Implant Failure Pathophysiology

Implanted metals corrode when in contact with biological fluids. Significant levels of metal ions have been found in capsular/periprosthetic tissues, in extracutaneous sites (liver, spleen, and lymph nodes) and in urine/serum of hip arthroplasty patients (6–12). Corrosion of stainless steel devices releases iron (Fe), chromium (Cr), molybdenum (Mo) and nickel (Ni) ions. Titanium (Ti) devices release Ti(IV), vanadium (V) and aluminium (Al) ions (13). Intravascular metal devices are often composed of nitinol (NiTi), stainless steel (NiCr, e.g. Society of Automotive Engineers – SAE 316L) or cobalt (Co) alloys. Nitinol releases the least amount of Ni, followed by CoCrNi alloys, whereas standard SAE 316L stainless steel tends to release the greatest amount of Ni (4). Metal release and endothelial cell exposure induces the expression of intercellular adhesion molecule type 1 but not cytotoxicity in an *in vivo* system (14). An autopsy study showed elevated tissue levels of Ni or Ti in cases with corroded/fractured cardiac stents (15). Released metal ions are processed by the immune system locally and at remote locations, potentially eliciting an immune reaction against the implanted metal alloy.

Cutaneous reactions above the implanted device are primarily T cell-mediated type IV delayed-type reactions. Reported reactions at the site of the metal implant include type IV reactions but are probably complex in nature. Peri-implant reactions seem to be Th1-dominant. The groups of Hallab and Thomas suggested that are increased levels of interferon (IFN)-γ and interleukin (IL)-6 in metal-allergic patients with joint arthroplasties (16, 17). Summer et al. found minimal IFN-γ but a significantly elevated level of IL-17 in Ni-allergic patients with symptomatic joint implants but not in Ni-allergic patients with well-functioning joint implants (18). Analyses of tissues adjacent to implanted metals in patients with metal hypersensitivity have shown elevated levels of immune cells/markers, including: CD3þ T lymphocytes, CD4þ cells, CD11cþ macrophages/dendritic cells, and cells with abundant major histocompatibility complex class II (human leukocyte antigen-DR) expression (dendritic cells) (13).

The innate immune system may also play a role in these reactions. The formation of foreign body giant cells is often seen when macrophages phagocytose foreign particles, including metals. These macrophages release proinflammatory cytokines (tumour necrosis factor-α, IL-6, IL-1α, and IL-1β) (13). Ti and V stimulate the production of superoxide anions in neutrophils, and Ni ions degrade neutrophil cell membranes at high concentrations (19, 20). The mechanism of pseudotumour formation and the development of aseptic lymphocytic vasculitis-associated lesions (ALVALs) is not known. Campbell et al. suggested that ALVALs can be histologically differentiated from failure resulting from high wear by use of an ALVAL scoring system. The infiltrate surrounding ALVALs adjacent to orthopaedic devices is a dense lymphocytic band interspersed with macrophages. This can be compared with a relatively macrophage-predominant infiltrate seen in patients with pain and high device wear (21).

A proposed mechanism for metal implant aseptic joint loosening was proposed by Cadosch et al. Osteoclasts are able to mature and proliferate on Ti and Al, leading to metal degradation, and uptake and eventual release of the Ti or Al ions. This mechanism might explain the increase in measurable metal ion levels in the systemic circulation. These osteolytic lesions may partially explain joint loosening (22). In addition to lytic/catabolic activity, hypersensitivity reactions may also occur because of the elevated ion levels and immune stimulation, leading to loosening of the implanted devices as supporting surrounding bone is resorbed. CCL17/TARC, CCL22/MDC, RANK-L, macrophage colony-stimulating factor and proinflammatory cytokines, including CCR4, are elevated in this peri-implant environment (23). CCR4 is also involved in the inflammatory reaction in cutaneous allergic contact dermatitis reactions (23, 24). Although this link between allergic cutaneous reactions and CCR4 or other proinflammatory cytokines is not proven, this area represents an important area of further inquiry. Also, these pathomechanisms may occur for other alloys as well.

Patch test reactivity to metals in those with implant failure may result from prior or current overload of metal ions in the system. One mechanism could be cutaneous

sensitization of T cells in the skin following presentation of metal ions by cutaneous dendritic cells/antigen-presenting cells. Although it has never been proven, we consider that antecedent metal allergy may be a risk factor for implanted device failure and/or hypersensitivity reactions if the individual was exposed to metals at some point at concentrations that resulted in elevated systemic metal levels with resultant sensitization of tissue dendritic cells in, for example, the bones as well as the skin. Alternatively, elevated metal ion levels in the adjacent bone following a metal implant allows bone dendritic cells to process and present metal allergens, leading to remote T cell sensitivity (i.e. cutaneous hypersensitivity and positive skin patch test reactions). The immunological environment in patients with idiopathic osteoarthritis of the hip is predominantly composed of type 1 lymphocytes associated with delayed-type reactions (25, 26). This may also predispose to local sensitization (27). The patch test reaction on the back is probably a direct re-creation of the type 4 reaction at a distant site, which is directly relevant to joint pathology.

Overview of Adverse Reactions to Implanted Devices

Metals are used extensively in medically implanted devices across specialties, including: orthopaedics, cardiovascular, gynaecology, and dentistry. These adverse reactions have been detailed by Basko-Plluska et al. (3). Therefore, this section will briefly summarize these reactions. The most commonly used metal alloys used across specialties are summarized in Table 1.

Orthopaedic – dynamic joints

Delayed-type hypersensitivity reactions to metals cause up to 5% of all total joint arthroplasty failures (30). One study found a linear correlation between lymphocyte reactivity and serum metal ion levels, suggesting a direct correlation with metal hypersensitivity (31). Metal patch test positivity is more common in those with revised metal-on-metal arthroplasties than in controls (32, 33). ALVAL is a rare finding that is non-specific and may be a systemic delayed-type hypersensitivity reaction. This has been reported in multiple cases of total joint arthroplasty failure (3). Local pseudotumours are rare findings, and are not clearly associated with hypersensitivity reactions. Common causes of non-allergic failure of total joint arthroplasties are reported to be infection, recurrent dislocation, aseptic osteolysis, and fractures. Symptoms of hypersensitivity are similar, including implant loosening, joint pain, and a cutaneous reaction at the implant site.

Orthopaedic – static implants

Static implants such as screws or plates are made of similar alloys to those used in dynamic implants. Nuss bars are used for *pes excavatum* repair and are available in stainless steel. Similar reactions occur adjacent to the static implants, leading to poor wound healing, chronic inflammation, and cutaneous findings such as dermatitis above or adjacent to the implanted metal.

Intravascular devices (stents, occluders, and endovascular devices)

Hypersensitivity reactions to intravascular devices occur. In-stent restenosis (ISR) arises in bare-metal stents in 16–33% of cases, and metal hypersensitivity may play a role in restenosis (4). It is unclear whether metal allergy directly causes ISR; in one investigation, all patients (10/121) with positive metal patch test results following implantation of a bare-metal SAE 316L stainless steel coronary stent were found to have ISR by angiogram 6 months after implantation. Although this number is impressive, in the same study, 57% (69/121) of those without positive patch test results had findings of ISR (34).

Another perspective was reported by Thyssen et al. Of 18 794 patients who were patch tested between 1979 and 2007, 149 (0.8%) were patch tested prior to placement of a metal stent. Fourteen per cent (21/149) of this group had ISR, but only 2 of 21 of those with ISR had metal allergy. These results did not support metal allergy being the cause of ISR (35). Gold-plated stents were initially used on the hypothesis that gold was an inert metal, and less likely to cause inflammation or local reaction in the vessel. Subsequent studies showed that gold exposure in cardiac stents was a strong risk factor for ISR, especially in those with prior gold allergy (36).

For a detailed and thorough discussion of this topic, see the review of Honari et al. and subsequent studies (4, 35, 37). Overall, it seems that Ni allergy is not a risk factor for ISR (following stenting with stainless steel stents), whereas gold allergy seems to be a relatively strong risk factor in patients with gold stents. For these reasons, the use of gold stents has been abandoned.

Pacemakers/defibrillators

Allergic complications following insertion of a pacemaker are rare, with ~30 cases reported in the literature (4, 30, 38). There are many components that could potentially cause contact allergy, but the Ti alloy shell is the most frequent cause (4). Components of pacemakers/defibrillators that are potential allergens and those

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Table 1. Metals/elements in selected alloys that are used in medical implants; variations of content exist, and the distribution offered is considered to be typical for each alloy

Implant alloy	Alloy elements	Approximate percentage	Use
Stainless steel SAE 316L	Iron	Balance	Cardiac/intravascular devices
	Nickel	8.3–35	Orthopaedic prostheses, plates, pins, nails, bolts, screws, and fixators
	Chromium	20	
	Manganese	2	
	Molybdenum	2–3	
	Nitrogen	0.1	Surgical clips/staples
	Carbon	0.03	
	Sulfur	0.03	
	Silicon	0.75	
	Phosphorus	0.045	
Cobalt–chromium–molybdenum steel	Cobalt	Balance	Cardiac/intravascular devices
	Chromium	27–30	Orthopaedic prostheses, plates, pins, nails, bolts, screws, and fixators
	Molybdenum	5–7	
	Nickel	<0.5	
	Iron	<0.75	
	Carbon	<0.35	Dental implants and restorations
	Silicon	<1	
	Manganese	<1	
	Tungsten	<0.2	
	Phosphorus	<0.02	
	Sulfur	<0.01	
	Nitrogen	<0.25	
	Aluminium	<0.1	
	Titanium	<0.1	
	Boron	<0.01	
Vitallium™	Cobalt	61	Orthopaedic prostheses, plates, pins, nails, bolts, screws, and fixators
	Chromium	32	
	Silicon	0.5	
	Manganese	0.5	
	Carbon	0.02	
	Boron	0.1	
	Molybdenum	5.6	
	Iron	None	
Titanium alloy	Titanium	89.9	Orthopaedic prostheses, plates, pins, nails, bolts, screws, and fixators
	Aluminium	5.5–6.5	
	Vanadium	3.5–4.5	
	Nickel	~0.012–0.034 (28)	Pacemaker shells
			Surgical clips/staples
Titanium–tantalum–niobium (29)	Titanium	53	Orthopaedic devices
	Niobium	25	
	Tantalum	7	
	Zirconium	5	
Nitinol	Titanium	55	Cardiac/intravascular devices
	Nickel	45	Patent foramen ovale and septal defect devices and implants
			Bone anchors and staples
			Essure® contraceptive device
			Urological devices
			Orthodontics
Oxinium™	Zirconium (oxidized)	97.5	Orthopaedic joint prostheses
	Niobium	2.5	

Modified from Basko-Plluska et al. (3).

reported to cause allergic contact dermatitis are summarized in Table 2.

Reactions usually take the form of dermatitis, localized to the area above implantation. Impaired wound healing may also occur. The majority of site reactions are infections, although metal hypersensitivity reactions may be misdiagnosed as infection (4, 39). An uncommon presentation is generalized or remote site dermatitis.

Table 2. Allergens in pacemakers/defibrillators

Confirmed allergens in pacemaker/defibrillator devices	Unconfirmed allergens in pacemaker/defibrillator devices
Wire/electrodes	
Silicone (polydimethylsiloxane)	Molybdenum
Nickel	Silver
Cobalt	Iridium
Chromium	Platinum
Palladium	Tantalum
Leads	
Polyurethane	Polytetrafluoroethylene
Silicone	—
Parylene (polychloroparaxylene)	—
Shell	
Titanium	Vanadium
Aluminium	—
Other	
Rubber accelerator (thiuram)	—
Epoxy resin	—
Epoxy hardener (triethylenetetramine)	—
Mercury	—

Gynaecological devices

Implanted metals in gynaecology are mostly from contraceptive devices. Intrauterine contraceptive devices (IUCDs) containing copper are used for temporary contraception. There are at least three cases of systemic allergic dermatitis resulting from IUCDs, which resolved with removal (3). The copper IUCDs, such as Paragard™ 380A (Duramed Pharmaceuticals, Tonawanda, New York, USA), contain polyethylene, barium sulfate, and 99.9% pure copper wire (possible contaminants include Ni, Zn, and Mn) (personal communication, Paragard Corp., 3 December 2010) (40). Copper allergy is a contraindication to placement. A newer, permanent device is Essure (Conceptus, Mountainview, CA, USA). These devices are implanted nitinol (55% Ti/45% Ni) outer coils with an SAE 316L stainless steel inner coil. These are placed and permanently expanded in the fallopian tubes. Ni allergy is a contraindication to placement (41) (personal communication, Conceptus Inc., 27 June 2011).

Dental

Dental implants, including orthodontic devices, are sources of metal exposure. For the purposes of this review, this topic will be covered only briefly. Potential allergen groups include metal alloys with Ni–palladium and/or Ti alloys, CoCrMo alloys, epoxy and epoxy-acrylate preparations, and a wide variety of other preparations, including anaesthetics and flavourings. Co-containing alloys are increasingly used as substitutes for the more expensive precious metal alloys. Co is released and is available in ion form from dental restorations (42). There are many commercially available patch test series that offer appropriate basic evaluation for individuals with potential reactions to dental-related devices. In addition to a commercially available dental screening series such as that shown in Table 3, our suggestions for further dental screening allergens are included in Table 4.

Table 3. A commercially available dental screening series

1. Methyl methacrylate 2.0% pet.
2. Triethyleneglycol dimethacrylate 2.0% pet.
3. Urethane dimethacrylate 2.0% pet.
4. Ethyleneglycol dimethacrylate 2.0% pet.
5. BIS-GMA 2.0% pet.
6. *N*,*N*-Dimethyl-4-toluidine 5.0% pet.
7. 2-Hydroxy-4-methoxy-benzophenone 10.0% pet.
8. 1,4-Butanediol dimethacrylate 2.0% pet.
9. BIS-MA 2.0% pet.
10. Potassium dichromate 0.5% pet.
11. Mercury 0.5% pet.
12. Cobalt(II) chloride hexahydrate 1.0% pet.
13. 2-Hydroxyethyl methacrylate 2.0% pet.
14. Gold sodium thiosulfate 2.0% pet.
15. Nickel sulfate hexahydrate 5.0% pet.
16. Eugenol 2.0% pet.
17. Colophonium 20.0% pet.
18. *N*-Ethyl-4-toluenesulfonamide 0.1% pet.
19. Formaldehyde 1.0% aq. **(authors recommend 2%)**
20. 4-Tolyldiethanolamine 2.0% pet.
21. Copper sulfate 2.0% pet.
22. Methylhydroquinone 1.0 pet.
23. Palladium chloride 2.0% pet. **(authors recommend 1%)**
24. Aluminium chloride hexahydrate 2.0% pet.
25. Camphoroquinone 1.0% pet.
26. *N*,*N*-Dimethylaminoethyl methacrylate 0.2% pet.
27. 1,6-Hexanediol diacrylate 0.1% pet.
28. 2(2-Hydroxy-5-methylphenyl)benzotriazol 1.0% pet.
29. Tetrahydrofurfuryl methacrylate 2.0% pet.
30. Tin 50.0% pet.

BIS-GMA, 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl] propane; BIS-MA, 2,2-bis[4-(methacryloxy)phenyl]-propane; aq., aqueous; pet., petrolatum.
Chemotechnique Diagnostics®; Vellinge, Sweden – reproduced with permission (43).

Should allergy screening be performed?

This is a complex topic that remains subjective. For this reason, we have recently reviewed the scientific evidence (5). Most agree that individuals without a reported history of metal hypersensitivity reactions (costume jewellery or other metal dermatitis) need not be screened prior to device implantation. A recent study patch tested 22 patients with self-reported metal reactions prior to

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Table 4. Additional dental allergens to consider

Allergen	Availability
2,2-Bis[4-(2-methacryl-oxyethoxy)phenyl]-propane 2% pet.	C
Ammonium hexachloroplatinate 0.1% aq.	C
Ammonium tetrachloroplatinate 0.25% pet.	A, C
Barium chloride 0.5% and 1% aq.	NA
Beryllium	NA
Cadmium chloride 1% aq.	A, C
Carvone 5% pet.	C
Gallium oxide 1% pet.	A
Indium chloride 10% aq.	C
Iridium chloride 1% pet.	C
Iron(III) chloride 2% aq.	A
Manganese chloride 0.5% aq.	A
Manganese chloride 2% pet.	C
Molybdenum(V) chloride 0.5% pet.	A
Niobium	NA
Rhodium	NA
Ruthenium 0.1% pet.	A
Silver nitrate 1% aq.	C
Titanium nitride 5% pet.	C
Titanium oxalate 5% pet.	C
Titanium oxide 0.1% pet.	A
Titanium powder 10% pet.	C
Vanadium trichloride 5% pet.	C
Zinc oxide 2% pet.	C
Zirconium(IV) oxide 0.1% pet.	A
Zirconium chloride 1% pet.	C

A, Allergeaze; aq., aqueous; C, Chemotechnique; NA, not available; pet., petrolatum.

surgery. Eighty-three per cent had metal reactions, suggesting that patch testing would identify metal-allergic individuals (44). In general, individuals who should be screened prior to surgery are those reporting a history of metal sensitivity of a magnitude sufficient to cause concern to the patient or a healthcare provider (5).

An alternative view suggests that the patient's own history of metal reactions is not sufficiently predictive to warrant patch testing, and that the prevalence of reactions is high enough to warrant pre-implant evaluation (45). Carlsson and Möller followed 18 implanted patients with pre-implant-confirmed metal allergy (Ni, Co, or Cr) for a mean of 6.3 years (46). None of those individuals had systemic or cutaneous reactions. Pre-implant screening is not performed routinely in Sweden or Denmark for any patient, and not systematically in other locations (47). In the United States, some patch testers consider pre-implant patch testing (48). For those with post-implant joint pain, implant loosening, or unexplained cutaneous reaction at the implant site, the question of metal hypersensitivity is often an indication for evaluation (5).

Even given this, there is a rare subset of patients with metal hypersensitivity who will develop cutaneous and/or systemic reactions to implanted metals. If these individuals are to be identified and reactions prevented, patch testing must be performed prior to implantation. The risk of patch testing with an array of metals is low, and the benefit for sensitive individuals would be prevention of potentially significant morbidity (i.e. pain, dermatitis, joint failure, and multiple surgical procedures). Patch testing should be considered both for those patients with suspicion of pre-implant metal hypersensitivity and those with suspected reactions to metal alloy implants. It is for these controversial and challenging groups that we propose patch testing with an allergen series appropriate for the exposure(s).

Once a positive patch test reaction is identified prior to surgery, there are several issues to address. Which implant/device will give the patient the best outcome in terms of functionality/durability, and does a positive patch test reaction to a metal found in the 'best' device warrant using an inferior device? In our opinion, the decision regarding the 'best' device needs to be made by the patient's surgeon. The dermatologist's expertise is in identifying the allergic reactions and giving guidance on safe materials for implantation (i.e. negative reactions with the metal screening series). In most situations, deliberately implanting a material to which someone is allergic is not ideal, and will make the 'best' option a suboptimal option. Illustrative of this point were patients examined in a retrospective case–control study prior to total hip replacement and symptomatic and asymptomatic individuals after total hip replacement. Those with positive patch test reaction(s) to metals and a history of metal hypersensitivity had significantly shorter lifespans of their implants. Of individuals with positive test(s) for bone cement components, none had a stable implant at a 10-year endpoint (27). These findings have not been confirmed in a prospective study. Sensitization and subsequent hypersensitivity, regardless of time of onset, are important to evaluate and address. This supports testing of individuals who report a history of cutaneous reactions to metals or to bone cement components prior to device implantation, as well the evaluation of symptomatic individuals after implantation.

What is the benefit of the medical history?

In general, a patient's history of dermatitis caused by metal items does not always predict metal allergy, although it may be a useful and simple predictor. Investigators have attempted to determine whether simple screening

questions such as 'Are you nickel-allergic?' and/or 'Do you get rashes from metals?' are sensitive and specific for identifying metal-allergic individuals. The lack of a history of metal item dermatitis does not predict negative metal patch test reactions (45). The validity of self-reported nickel allergy was examined, and this showed a sensitivity and specificity of 37–82% and 77–87%, respectively (49–51). Only two patients (8.9%) reporting dermatitis from metal exposures (jewellery) did not have metal contact allergy (27).

Patch testing versus lymphocyte transformation test. Is the patch test useful?

Patch testing is an *in vivo* medical test for type IV reactions, whereas the lymphocyte transformation test (LTT) is an *in vitro* test. The LTT measures the proliferation of lymphocytes from peripheral blood in the presence and absence of a potential allergen after incubation for 7 days. The result is reported as a stimulation index. This method is proposed as an alternative to patch testing, but, at this time, it cannot be recommended in place of the gold standard – patch testing. This is because of the limited number of allergens that are tested, limited availability, and the rapid decay of T cells making rapid transportation a prerequisite. However, the LTT may be useful in doubtful/questionable cases for further evaluation or confirmation of one or several potential allergens (52, 53). Fifty-six individuals with Ti implants, systemic symptoms and negative patch test results were positive in a Ti LTT; 54 of 56 had the metal implant removed, and those 54 had complete resolution of symptoms (52). In the orthopaedic literature, some claim that the LTT better reflects immune reactions within the body, whereas the patch test mainly reflects cutaneous reactivity (53) The LTT's clinical significance in implant intolerance remains to be established.

Although patch testing is not a perfect investigation by itself, it offers a breadth of evaluation, ease of use and relatively widespread availability that are not available with the LTT (5). The patch test is primarily used to evaluate cutaneous reactions, and the test is performed on the skin; dermatitis should be evaluated by this test. The LTT only offers evaluation of reactions to circulating lymphocytes, and not those specifically targeted to the skin. As the majority of cutaneous and systemic reactions relating to metal hypersensitivity are type IV in nature, patch testing remains the gold standard, and should remain the primary diagnostic tool for allergic contact dermatitis. Other test systems, such as the LTT, need to be further validated, and the LTT may become a useful secondary test for hypersensitivity reactions if validity is confirmed. Prospective data, broader access and more generalized use are needed before the LTT can be routinely recommended. The LTT is available commercially as the MELISA™ test (Health Diagnostics and Research Institute, South Amboy, NJ, USA).

Issues related to testing in general and for metals specifically are:

(1) Irritancy of the metals tested – metal chlorides are irritant even at low concentrations (54).
(2) Patient sensitization from testing – the reported risk is low for most metals. Examples of relevant allergens reported to cause sensitization following patch testing are: cadmium, potassium dichromate, and methyl methacrylate (55). Ni is not a sensitizer when used for patch testing at 5% (56).
(3) Potential for false-positive/irritant (some metal salts), false-positive/pressure effect (metal discs) or false-negative test results (especially metal discs).
(4) Excited skin syndrome (angry back) leading to false-positive results.

Patch Test Series

Baseline series

In many cases, addition of a baseline series appropriate for the patients' geographical location [North American (NA) Standard or American Contact Dermatitis Society's Core Panel, European Baseline Series, etc.] is appropriate. Two reviews examining endovascular devices and metal device implantation have both suggested some form of baseline screening for all patients (4, 44). In individuals without a history of dermatitis, an abbreviated series such as the TRUE Test®, the European baseline series (Trolab®; Almirall Hermal GmbH, Reinbek, Germany, or Chemotechnique Diagnostics, Vellinge, Sweden) or the 50 allergens of the NA Standard series (Chemotechnique) may be adequate. In those with dermatitis, specialty trays appropriate for the clinical history and a full evaluation with an extended series such as the extended NA standard series (Chemotechnique or Allergeaze; SmartPractice, Calgary, AB, Canada) or the International Comprehensive Baseline series (Chemotechnique) are indicated.

If a patient is to be evaluated, comprehensive testing should be performed. Patch testing with a single allergen or a handful of allergens is not recommended. A single allergen or allergen group (i.e. metals) may not be the only cause of dermatitis. For example, a patient being treated for metal-related dermatitis over an implant with bacitracin or benzocaine may have a primary reaction from a metal allergen in the implant and a secondary reaction to the agent(s) being used for symptomatic relief.

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Metals

Proposed metals that should be considered for patch testing in patients undergoing evaluation for metal allergy prior to an orthopaedic implant or for metal implant failure are discussed in this section. It is impractical to suggest a single patch-testing series that is appropriate for all situations and implants (i.e. a generic prosthetic series), although various suggestions for prosthetic series exist (4, 44). These series are summarized in Table 5. Metals present in different types of implant or device and that potentially should be considered for diagnostic patch testing are summarized by metal and implant type in Table 6. The patch test battery should reflect the metals currently used in orthopaedic implants and be continuously updated.

Table 5. Prosthesis series suggested by other authors (4, 44)

Honari et al. (4)	Reed et al. (44)
Modified prosthesis series	Mayo prosthesis series
Ammonium molybdate 1% aq.	n-Butyl methacrylate 2% pet.
Bacitracin 20% pet.	1,4-Butanediol dimethacrylate 2% pet.
Chlorhexidine gluconate 0.5% aq.	4-*tert*-Butylphenol 1% pet.
Cobalt chloride 1% pet.	Benzoyl peroxide 1% pet.
Colophonium 20% pet.	Beryllium sulfate tetrahydrate 1% aq.
Formaldehyde 1% aq.	Bisphenol A 1% pet.
Gold sodium thiosulfate 0.5% pet.	Chromium chloride 5% pet.
Indium sulfate 10% aq.	Cobalt chloride 1% pet.
Iridium chloride 1% aq.	Cobalt chromium disc
Manganese chloride 2% aq.	Epoxy resin 1% pet.
Methyl methacrylate 2% pet.	Ethyl methacrylate 2% pet.
Neomycin sulfate 20% pet.	Ethylene glycol dimethacrylate 2% pet.
Nickel sulfate 2.5% pet.	Hydroquinone 1% pet.
Palladium chloride 1% pet.	2-Hydroxyethyl methacrylate 2% pet.
Polydimethylsiloxane 10% pet.	Methyl methacrylate 2% pet.
Potassium dichromate 0.25% pet.	Molybdenum chloride 1% pet.
Tantalum powder 1% pet.	Nickel sulfate hexahydrate 2.5% pet.
Titanium dioxide 10% pet.	Potassium dichromate 0.25% pet.
Titanium powder 1% pet.	Stainless steel (as is) (alloy varies by device)
—	Tetraethylene glycol dimethacrylate 2% pet.
—	Titanium alloy disc (alloy varies by device)
—	Triethylene glycol diacrylate 0.1% pet.
—	Triethylene glycol dimethacrylate 2% pet.
—	Vitallium™ (as is)

aq., aqueous; pet., petrolatum.

Our approach to patch testing of individuals with suspected metal allergies is based on the type of implant and the presence or absence of dermatitis. We have provided a list of patch test substances used for diagnosis of contact allergy to metals, summarized the evidence for the use of each metal and commented on recommended concentrations/vehicles in Table 7. The authors' opinions on the best screening allergen are in bold, when multiple allergens are available. Other substances that it is important to consider adding to the patch test tray are similarly summarized in Table 8. These series, like all special series, have not yet been evaluated for clinical significance.

Screening for allergies in relation to orthopaedic implants is based on the patient's presentation. Figure 1 breaks down the trays to consider them by patient presentation and implant type. Standard baseline screening series are recommended either as a baseline series (a focused set of allergens) or an extended series. Other series are suggested and are referred to in Tables 6–8. In some cases, samples of the actual material in question may be obtained and tested 'as is' on the skin. In many cases, a test kit can be obtained from the device manufacturer. It is possible to have false-positive pressure effects and false-negative reactions from testing metal discs. These 'test discs' are not adequate for complete testing, and may cause irritant/questionable reactions (57). Use of these kits is recommended, although with caution. In questionable cases, addition of an LTT should be considered.

If the history indicates more extensive testing, appropriate allergens should be added. These series are not meant to constitute a blanket recommendation for every single patient. Each individual should have a custom series suited to their own set of issues. We recommend using the figures/tables to identify appropriate allergens for your patient's unique situation.

Cement components

In many cases, orthopaedic implants are secured with bone cement. This material is composed of a methyl methacrylate, an *N*,*N*-dimethyl-*p*-toluidine reaction initiator, and a benzoyl peroxide activator. Hydroquinone is occasionally added as a stabilization agent for the methyl methacrylate. In Europe, antibiotic agents, especially gentamicin, are added to this mix. These agents are potential causes of contact allergy and of joint loosening, with 25% of patients in one series having reactions to bone cement components (85). Another series reported that 7 of 15 patients with early aseptic loosening of cemented total hip replacements had positive reactions to *N*,

Table 6. Substances that may be present in different types of implant or device and that potentially should be considered for diagnostic patch testing

		Implant or device				
		Orthopaedic				
Substances or alloy[a]	Dental	Pre-implant	Post-implant	Intravascular	Pacemaker and ICD	Gynaecological
Aluminium	x	x	x	—	x	—
Beryllium	x	—	—	—	—	—
Cadmium	x	—	—	—	—	—
Chromium	x	x	x	x	x	x
Cobalt	x	x	x	x	x	
Copper	x	—	—	—	—	x
Gold	x	—	—	x	—	—
Indium	x	—	—	—	—	—
Iridium	—	—	—	—	x	x
Iron	x	x	x	x	—	—
Manganese	x	x	x	x	—	x
Mercury	x	—	—	—	x	—
Molybdenum	x	x	x	x	x	—
Nickel	x	x	x	x	x	x
Niobium	x	x	x	—	—	—
Palladium	x	—	—	—	—	—
Phosphorus	x	x	x	—	—	—
Platinum	x	—	—	—	x	x
Rhodium	x	—	—	—	—	—
Ruthenium	x	—	—	—	—	—
Silicon	—	x	x	—	—	—
Silver	—	—	—	—	x	x
Tantalum	—	x	x	—	x	—
Tin	x	—	—	—	—	x
Titanium	x	x	x	x	x	x
Tungsten	—	x	—	x	—	—
Vanadium	x	x	x	—	x	—
Zinc	x	—	—	—	—	x
Zirconium	x	x	x	—	—	—
Custom-made disc of relevant alloy	x	x	x	x	x	—

ICD, implanted cardiac defibrillator.
[a]See Table 7 for patch test substance(s), including concentration, vehicle, and availability.

N-dimethyl-*p*-toluidine (84). No patients had reactions to methyl methacrylate, benzoyl peroxide, or metals. Another study reported that 25% of total hip replacement patients had positive patch test reactions to methyl methacrylate 6 months after implantation (89).

It is important to consider reactions to cement in symptomatic patients following a procedure using bone cement. In these symptomatic individuals, addition of bone cement components is indicated to allow for thorough evaluation. These suggested allergens and evidence for their use are summarized in Table 8.

Management

It is important to differentiate between a positive patch test reaction (contact allergy) and the clinical entity of allergic contact dermatitis. A positive patch test reaction alone is not enough to warrant changes in management in an asymptomatic patient. Only reactions that are clinically relevant in symptomatic patients should lead to intervention. For example, a patient with an asymptomatic knee or hip implant patch, tested for other reasons, who has a positive reaction to Ni should not have any intervention regarding the implant.

Few prospective trials or other consensus opinions give specific guidelines on management. A German consensus paper suggested the use of Ti implants for all patients with a history of metal allergy (90). For individuals with dermatitis for whom implant removal is not possible, one author suggested that a tapered dose of oral prednisone over 21 days may be helpful (91). Figure 2 summarizes our opinions (non-evidence-based) on the potential management of those with metal-allergic contact dermatitis and/or systemic hypersensitivity to metal ions.

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Table 7. Patch testing materials: – evidence for use in metal implants

Metal	Patch test substance	%	Vehicle	Availability	Evidence for use in implants (references)	Comments by the authors: opinions and comments
Aluminium	Aluminium	100	pet.	C	(58)	Aluminium chloride hexahydrate, preferable concentration 10%
	Aluminium hydroxide	10		A		
	Aluminium chloride hexahydrate	2		C		
Boron	Boron trifluoride ethylamine	1	pet.	NA	(55)	No evidence of contact allergy related to implanted joints. Reported contact allergy from epoxy hardening systems. Recommend testing at 1% pet.
Chromium	Chromium(II) sulfate	0.5	pet.	A	None	—
	Chromium(III) chloride	1	pet.	A	(59)	Wear-related ions may be more commonly trivalent chrome
	Potassium dichromate	0.25	pet.	C	(60)	0.5% preferable to 0.25% or 0.375%. Few irritant reactions, but more false negatives at lower concentrations
		0.5				
Cobalt	Cobalt(II) chloride hexahydrate	1	pet.	A, C	(61)	Reduction to 0.5% decreased reaction, but decreased sensitivity
Copper	Copper(I) oxide	1	pet.	C	—	—
	Copper sulfate	5		NA	(62, 63)	Copper used most commonly in implants.
		2	**pet.**	A, C		
		1	aq.	A, T		Irritant and pustular irritant reactions may occur at concentrations > 1.25–5%. 5% preferred concentration – no equivocal reactions, many at 2%
Gold	Gold sodium thiosulfate	0.25	**pet.**	T	(64)	0.5% pet. preferred
		0.5		A, C		
		2		C		
	Potassium dicyanoaurate	0.5	aq.	C	—	Less preferable than gold sodium thiosulfate
		0.002	pet.			
Indium	Indium chloride	1	pet.	A	(55)	10% aq. preferred
		10	**aq.**	C		
	Indium sulfate	10	aq.	C	(65)	Slightly more reactions in indium sulfate than in chloride in same patient
Iridium	Iridium	1	pet.	C	None	—
	Iridium chloride	1	aq.	A, C	(65)	Iridium chloride superior to ammonium hexachloroiridate
			pet.			
	Ammonium hexachloroiridate	0.1	aq.	C	(65)	—
Iron	Iron(III) chloride	**2**	pet.	C	(66)	2% aq. showed more consistent positives than 1%
			aq.	A		
Manganese	Manganese chloride	0.5	aq.	A	None	—
		2	pet.	C		
Mercury	Mercury	0.5	pet.	A, C	None	—
	Mercuric chloride	0.1	pet.	C	(67)	Irritant, but necessary for thorough mercury testing
	Ammoniated mercury	1	pet.	T	—	Dental allergen
Molybdenum	Molybdenum(V) chloride	0.5	pet.	A	(68)	Irritating if tested at >2%
	Molybdenum	5	pet.	C	—	—

Table 7. *Continued*

Metal	Patch test substance	%	Vehicle	Availability	Evidence for use in implants (references)	Comments by the authors: opinions and comments
	Ammonium molybdate tetrahydrate	1	aq.	C	(55)	—
	Ammonium heptamolybdate	1	aq.	A	(55)	1% pet. base recommended
Nickel	Nickel sulfate	2.5 **5**	**pet.**	A, C, T	(69–71)	Consider 10% in clear cases that are negative at 2.5% and 5%. Nickel chloride more irritating than sulfate. Testing at 2.5% misses 20% of the positives found at 5%
Niobium	Niobium	NA	NA	NA	None	Used in newer metal alloys. No reports of allergy
Palladium	Palladium chloride	1 2	pet.	A, T C	(72) —	Sodium tetrachloropalladate covers all palladium chloride reactions plus 14% more
	Sodium tetrachloropalladate	**3**	**pet.**	NA		—
Phosphorus	Phosphorus sesquisulfide	0.5	pet.	C	(73)	Relevant allergen in matchhead dermatitis. No clear linkage to implanted metal alloys
Platinum	Ammonium hexachloroplatinate	0.1	aq.	C	(55)	Platinum salts may cause type I reactions. Both concentrations recommended
	Ammonium tetrachloroplatinate	0.25	pet.	A, C, T		
Silver	Silver nitrate	1	pet. aq.	C A	(67)	Irritant
Tantalum	Tantalum	1	pet.	A	(55, 73)	Tested at 1% pet. – 2+ reaction in one case
Tin	Tin(II) chloride	**1**	**pet.**	**T**	None	Probably a low-frequency allergen. No clear recommendations for testing
	Tin	**50**	**pet.**	C		
Titanium	Titanium(IV) chloride	**0.1**	**pet.**	NA	(74)	$TiCl_4$ 0.1% pet. preferred over testing with Ti powder
	Titanium nitride	5	pet.	C	(43)	Used in medical devices/bioimplants
	Titanium oxalate	5	pet.	C	(43)	Dental alloys
	Titanium oxide	**0.1** 10	**pet.**	A C	(55)	0.1% or 5% recommended
	Titanium powder	10	pet.	C	(55)	Elemental Ti can be tested at 100%
	Calcium titanate	10	pet.	C	(43)	Dental alloys
Tungsten	Tungsten	5	pet.	C	(75)	Sodium tungstate – minimal allergen in tungsten-exposed workers. Cause of pustular irritant reaction. Recommend aq. testing to decrease irritancy
Vanadium	Vanadium trichloride	**5** 10	**pet.**	C A	(68)	Irritating if tested at >2%
Zinc	Zinc	10	pet.	C	—	—
	Zinc chloride	2	pet.	C	(76)	One case of systemic allergic contact dermatitis, confirmed with 2% pet.
Zirconium	Zirconium(IV) oxide	0.1	pet.	A	(55)	—
	Zirconium chloride	1	pet.	C	(77, 78)	Zirconium chloride considered to be a 'non-sensitizer'. Added to bone cement as radio-opaque material

A, Allergeaze; aq., aqueous; C, Chemotechnique; NA, not available; pet., petrolatum; T, Trolab/Hermal.

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Table 8. Patch testing materials: other components – evidence for use in testing

Allergen	%	Vehicle	Availability	Evidence	Comments
Pacemakers/ICD					
Epoxy resin, bisphenol A	1	pet.	C	(4)	—
Polychloroparaxylene (parylene)	100	—	NA	(79)	Has been stripped from the underlying metal and tested as is
Polydimethylsiloxane (silicone)	10	pet.	NA	(4)	No commercial allergen available. Also consider testing as is from device test kit
PTFE (Teflon)	—	—	NA	(80)	No reports of allergy. PTFE pouch used successfully to prevent reactions to allergenic pacemaker
Polyurethane	—	—	—	(81)	—
4,4-Diaminodiphenylmethane	0.5	pet.	C	(82)	Consider diluting to 0.25% to limit patch test sensitization, but this increases the risk of false-negative reactions
Diphenylmethane-4, 4-diisocyanate	2 1 **0.5**	pet.	C A **NA**	(82) (Hamada, personal communication, 2011)	Testing at 0.5% recommended. If possible, allergen blends prepared with polymeric diphenylmethane diisocyanate with 35% DMA monomer are preferable
Isophorone diisocyanate	1	pet.	C	(81)	—
Toluene-2,4-diisocyanate	**2** 1	**pet.**	C A	(81)	—
Thiuram (rubber accelerator)	1	pet.	C, A	(4)	Single case report of thiuram mix positivity reported
Triethylenetetramine (epoxy hardener)	0.5	pet.	C, A	(83)	—
Bone cement components					
Methyl methacrylate monomer	2	pet.	C, T, A	(84)	Risk of patch testing sensitization if tested at 100% (55). Add to chamber at time of testing – not before. Early loading may cause false negatives (72)
n-Butyl methacrylate	2	pet.	C	(85)	—
Polymethylmethacrylate polymer	100	—	NA	Rare allergen (3)	Test 'as is' (55)
Benzoyl peroxide	1	pet.	C, T, A	(85)	—
N,*N*,-Dimethyl-*p*-toluidine	5 **2** 0.5	pet.	C **A, T** NA	(86)	High prevalence of allergic contact dermatitis in symptomatic total hip replacement. 2% recommended by ICDRG (55)
Hydroquinone	1	pet.	A, C	(85)	—
Gentamicin	20	pet.	A, C, T	(85)	—
Tobramycin	20	pet. or aq.	NA	(55, 85)	—
Vancomycin	10	aq.	NA	(87)	—
Barium sulfate	2	aq.	NA	(85, 88, 89)	Mix fresh prior to use. Rare cause of allergic contact dermatitis
Zirconium chloride	1	pet.	C	(85)	—
Zirconium oxide	0.1		A		
Polyethylene	100	—	NA	(4)	Unclear test method, but they patch tested with the polyethylene backing. If necessary, obtain and use 'as is'

A, Allergeaze; aq., aqueous; C, Chemotechnique; DMA, Diphenylmethane-4, 4-diisocyanate; ICD, implanted cardiac defibrillator; ICDRG, International Contact Dermatitis Research Group; NA, not available; pet., petrolatum; PTFE, polytetrafluoroethylene; T, Trolab/Hermal.

Conclusion

Patch testing is the gold standard for evaluation of type IV hypersensitivity reactions. Appropriate and extensive patch testing is indicated in patients with implanted metal devices and suspected metal hypersensitivity reactions. Although routine pre-implant patch testing is not recommended, there is a subset of individuals with a prior history of reported

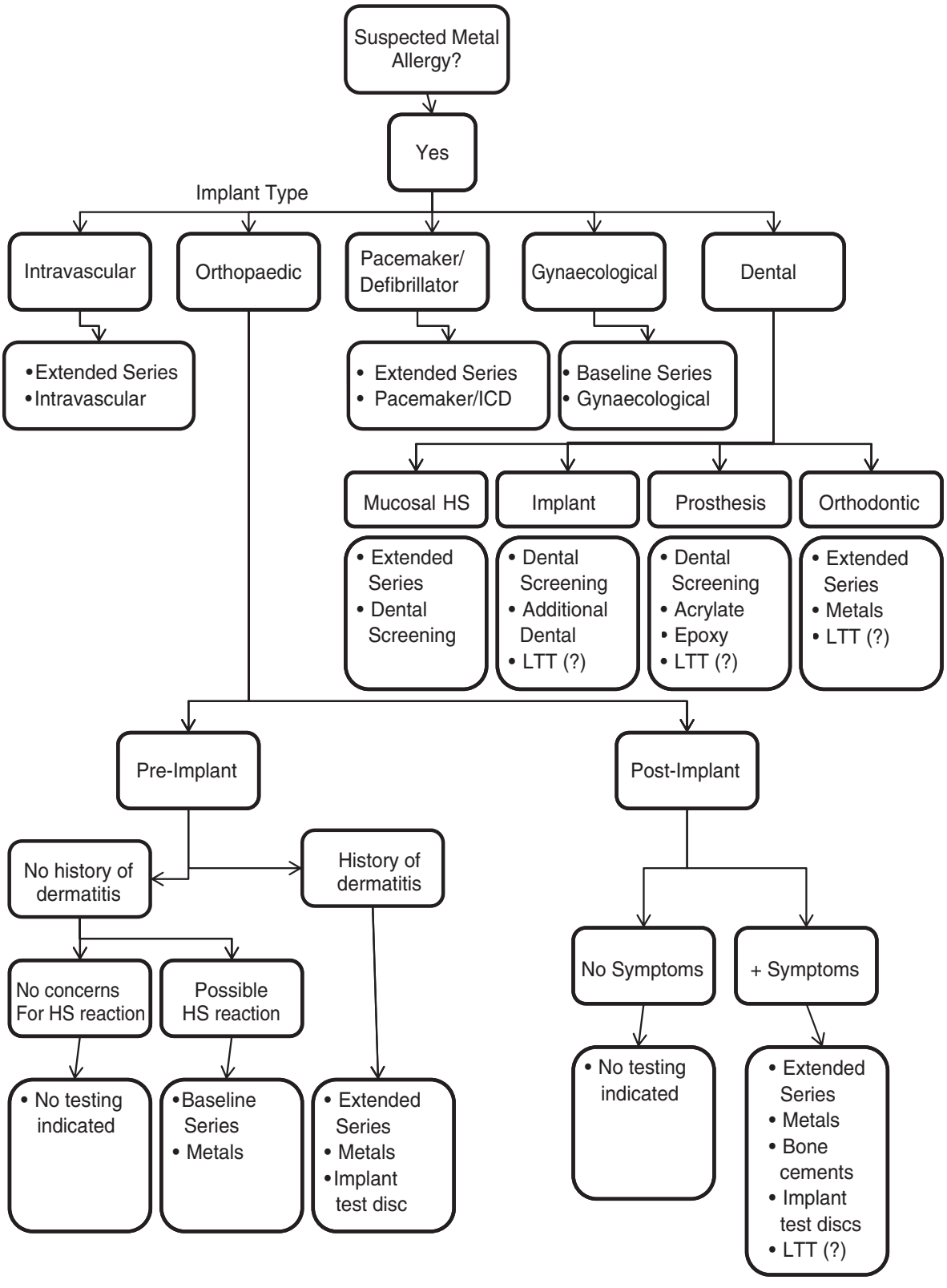

Fig. 1. Diagnostic algorithm for the evaluation of suspected metal allergy. HS, hypersensitivity; LTT, lymphocyte transformation test.

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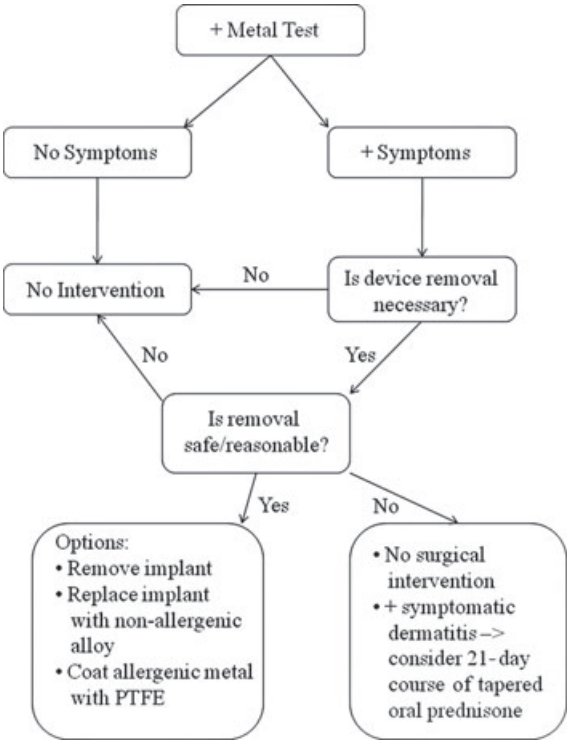

Fig. 2. Management algorithm for metal hypersensitivity reactions. PTFE, polytetrafluoroethylene.

cutaneous metal hypersensitivity who should be patch tested prior to device implantation. Use of the tables and patient selection algorithms should make the patient selection for testing and allergens that is necessary for thorough evaluation simple and clear. Management following diagnosis of metal hypersensitivity is controversial. There are no objective criteria for determining which patients should undergo additional surgery, with the unavoidable risks and discomforts involved.

There are two final considerations regarding the approach to potentially metal-allergic patients. First, a positive patch test result (an immunological process) is not necessarily relevant to a clinical disease process (allergic contact dermatitis and symptoms such as joint loosening). Do not make management decisions on the basis of a positive test result alone. Second, there are few prospective data available that meet the diagnostic postulates suggested by Thyssen on which to base decisions in these challenging patients (5). Prospective trials are needed to closely examine these patients and provide evidence for an evidence-based approach.

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