

Prosthetic and Device Surgery Considerations

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Abbreviations *ACD* Allergic contact dermatitis · *ASD* Atrial septal defect · *AJL* Aseptic joint loosening · *ALVAL* Aseptic lymphocytic vasculitis associated lesion · *BMS* Bare metal stent(s) · *ICD* Intracardiac defibrillator · *ISR* In-stent restenosis · *IUD* Intrauterine device · *DES* Drug eluting stent(s) · *CoCrMb* Cobalt chromium molybdenum · *LTT* Lymphocyte transformation test · *MHR* Metal hypersensitivity reaction · *PFO* Patent foramen ovale · *PT* Patch testing

Opinion Statement

Biomedical implants have a broad array of therapeutic uses, most commonly in orthopedic procedures, such as dynamic hip and knee replacements. There are also wide-ranging applications in cardiology, gynecology, and other specialties. Use of metal components will likely expand with further medical innovations. Hypersensitivity reactions to these devices are well documented but uncommon. Patch testing is currently the best evaluation for metal hypersensitivity reactions (MHR). Preimplant testing for asymptomatic individuals is not necessary. Patients with a history of skin rashes dermatitis after metal contact would likely benefit from preimplant testing. Those individuals with postoperative complications such as aseptic loosening; chronic pain; or new, unexplained local or regional dermatitis may benefit from evaluation for MHR. Metal allergy testing is never indicated in emergent or life-threatening situations. Whether prior to or after implant placement, collaborative efforts between the allergist and surgeon should determine the clinical plan. A positive test for metal allergy should not define treatment. When a metal allergy is revealed prior to implant, every effort should be taken to avoid the allergen(s). Often, titanium or oxidized zirconium alloys are the most appropriate choice for those allergic to stainless steel components. Clinical decision making after implantation is challenging. If the implant is asymptomatic, no action should be taken. Symptomatic patients following implant are more challenging. The surgeon and patient need to determine whether replacement with a non-allergenic alternative is feasible, necessary, and safe. Prospective

trials in this field are still necessary to develop a more evolved and evidence-based approach to treatment of patients with MHR.

Introduction

Delayed-type hypersensitivity to implanted metallic biomedical devices is well documented, albeit uncommon. Metal hypersensitivity reactions (MHRs) are associated with poor wound healing and joint loosening, although it is unclear if the relationship is causal. Overall, described reactions are broad, with common cutaneous symptoms including dermatitis above or regionally to the implant site and poor wound healing. Pain, implant loosening, and instability to abject device failure are the most common internal presentations. As the population ages and the utility of biomedical devices increases, understanding immunologic reactions to such devices

becomes a topic of concern in optimizing patient care. Metals and metal alloys are utilized in a wide array of medical fields, including cardiology, gynecology, neurosurgery, orthopedics, and dental surgery. Common devices include pacemakers, intracardiac defibrillators, coronary stents, contraceptive devices (Essure (Bayer, Inc) and intrauterine devices), as well as orthopedic joints, screws, and plates. This review aims to serve as an update of the current knowledge in the field and serve as a guideline for healthcare providers who tend to the ever-growing population of patients with biomedical devices.

Metal allergy

Allergic contact dermatitis (ACD) has been reported from metals such as nickel, gold, cobalt, mercury, copper, chromium, and aluminum [1]. Allergic reactions to metals are common, as it is estimated that up to 17 % of women and 3 % of men are allergic to nickel, and 1–3 % are allergic to cobalt and/or chromium [2, 3]. Repeated exposure to common consumer items such as jewelry, cell phones, tools, utensils, laptops, and coins may provoke sensitization and further elicitation of cutaneous ACD [4, 5]. There are no reliable estimates of the prevalence of other metal allergies such as to titanium, molybdenum, aluminum, or vanadium.

Systemic reactions to metal exposures, such as systemic nickel allergy syndrome (SNAS), are not well understood and the literature controversial. Nickel is the most established ingested allergen, through ingestion of foods such as peanuts, cocoa, chocolate, oats, beans, salmon, cashews, and mackerel, all of which have a high content of nickel [6]. In one study, 80 % of patients with proven nickel sensitivity achieved full resolution of symptoms with a low-nickel content diet [7]. A point system for avoiding nickel ingestion may be helpful [8] and a low cobalt diet may help in some cases of dyshidrosis [9]. Information on reactions to other ingested metals is sparse.

Immune response to metallic implants

The immunologic response to metal implants is diverse and attributed to both the innate and adaptive immune systems. Cutaneous reactions most frequently manifest as eczematous eruptions or urticaria. Peri-implant reactions include

aseptic loosening, pseudotumor formation, and aseptic lymphocytic vasculitis associated lesions (ALVALs) [10, 11]. A recent systematic review found the pooled estimate incidence of metal implant-related ALVAL to be 0.6 % [12]. A recent case study reported a Marjolin ulcer that developed in the setting of chronic ACD following orthopedic implant [13•]. Despite its diversity, the most common type of cutaneous allergic reactions associated with metal implants are eczematous reactions occurring either locally in the area of skin overlying the device site or generalized.

Pathophysiology

Though the pathophysiology of metal allergy is not entirely clear, it is known that the wear and subsequent corrosion of metallic implants leads to free metal ion release. Increased metal ion levels are found in periprosthetic spaces, remotely in serum and urine, and in extracutaneous sites such as liver, spleen, and kidney tissue [14–20]. Metal release tends to be highest during the weeks after implantation. Following contact with biologic fluids, stainless steel releases chromium (Cr), molybdenum (Mo), nickel (Ni), and iron (Fe) ions, and titanium alloys release titanium, vanadium, and aluminum [21]. Nitinol releases the least nickel, stainless steel the most. However, it has been shown that some low-sulfur gradations of stainless steel release very small amounts of nickel and do not elicit reactions in sensitized patients [20]. These free metal ions are processed immunologically both at the prosthetic site and remote locations eliciting responses to the metal alloy [22, 23••].

Localized cutaneous reactions to implanted devices are attributed to the adaptive immune response, or more specifically, type-IV delayed hypersensitivity reaction. These responses are Th1-cell dominant and caused by antigen-presenting cells, after sensitization to metals as mentioned above. Many studies have shown the increased activity of IFN-gamma, further suggesting the adaptive immune response to implants [24, 25]. Other studies have shown that peri-implant tissue in patients with metal hypersensitivity have increased levels of other immune cells/markers such as CD3b T lymphocytes, CD4b cells, and CD11 cb macrophages/dendritic cells [21].

Besides cutaneous reactions, adverse events such as aseptic loosening of prosthetic joints or in-stent cardiac restenosis occur following metal device implantation. The role of the innate immune system in these unfortunate reactions is a continually evolving field. A consensus of recent studies agrees that free metal debris acts as both danger-associated (DAMP) and pathogen-associated (PAMP) molecular patterns, eliciting a cytokine-based inflammatory response [25]. Similarly, other studies hypothesize that free nickel and cobalt ions conjugate with peptides, become haptens, and act as superantigens [24, 25, 26••]. These immunogenic entities activate danger signaling via the inflammasome and pathogen signaling via the NF-KB pathway. This causes downstream expression of the inflammatory mediators intercellular adhesion molecular type 1 (ICAM1), IL-1b, and TFN-alpha [27–29].

One study posits that periprosthetic nickel and cobalt can directly stimulate human toll-like receptor 4, leading to a massive production of proinflammatory chemokines. Similarly, Lawrence et al. suggests that the inhibition of this receptor at specific histidine sites may even be a potential strategy for

therapeutic intervention for metal implant hypersensitivity [30, 31].

In most orthopedic implantations, metallic surfaces freely interact with surrounding biologic fluid. Cadosch et al. reported evidence that osteoclast precursor cells mature and differentiate on surgical stainless steel, titanium, and aluminum [14]. These matured osteoclasts corrode metal surfaces and release free metal ions into the peri-implant space. This is consistent with the finding of metallic debris both in periprosthetic tissue and remotely from spread via lymphatics and vasculature. Free metal ions bind to endogenous proteins, generate immune reactions, and recruit proinflammatory cytokines [21]. One such example is CCR4, a chemokine receptor known to be involved in allergic cutaneous reactions and one that functions to recruit helper T-cells [14, 32, 33]. This may explain why periprosthetic tissue examined after implant failure exhibits T- and B-lymphocyte proliferation [21, 23••, 25]. Accordingly, some estimate that type IV hypersensitivity to free metal ions is responsible for 1–5 % of joint arthroplasty failure in older implants [34••].

Besides the role of cell-mediated immunity, there is also a growing interest in the concomitant role of the innate immune response in MHR. A recent paper suggests that implant debris recruits macrophages and osteoclasts to periprosthetic regions, causing bone resorption via *nf-kb* ligand (RANKL) signaling, therefore contributing to implant destabilization [31]. Others suggest that the *NALP3* inflammasome within macrophages is the critical mediator of osteolysis [35].

Autopsy reports have shown increased amounts of tissue Ni and Ti in cases with corroded and fractured cardiac stents [36]. Subsequent studies argue that endothelial cell exposure to nickel and subsequent recruitment of ICAM-1 leads to fibrosis and subsequently in stent restenosis of cobalt/chromium coronary devices [32]. There remains a lack of in vivo studies to identify whether the currently proposed mechanisms are the direct cause of implant-associated reactions and failure. Cytokine-based clinical and basic science studies are in progress to provide therapeutic intervention strategies [31].

Gynecologic devices

Nickel, copper, and titanium are used in contraceptive devices placed in the uterus or fallopian tubes. IUDs are now the most commonly used method of reversible contraception worldwide, used by an average of 23 % of female contraceptive users [37, 38]. Copper-sulfate IUDs, such as Paragard (380A Duramed Pharmaceuticals, Tonawanda, New York, USA), are made of 99.8 % copper wire, polyethylene, and barium sulfate. IUDs rarely cause systemic dermatitis, with only five case reports ranging from 1976 to the present. In all such cases, patients had a positive patch test to copper sulfate and complete resolution after removal of the IUD [39–43]. Essure (Bayer, NJ, USA), a method for permanent contraception, is implanted transvaginally into the proximal fallopian tube and expanded during an in-office procedure. Scarring subsequently occludes the fallopian tube, achieving permanent contraception [44]. The Essure consists of an inner coil of stainless steel and polyethylene terephthalate fibers and an outer coil of nitinol. Nickel allergy initially was a contraindication to placement, but in 2011, the US Food and Drug Administration (FDA) removed this recommendation, as reported device-related

adverse events to the FDA had been low [45]. Zurawin et al. determined the adverse reactions related to nickel hypersensitivity to be about 0.01 % from a review of the SEER database [46]. Case reports demonstrate possible Essure-related dermatitis secondary to the nickel component of the device, with three reported cases of ACD, all of which resolved with removal of the insert [47–50]. In February 2016, the FDA announced the addition of a warning label, a formal consent process, and a postmarket study of Essure complications [51].

Cardiac devices

Coronary stents

Cardiovascular disease remains the number one cause of death globally, with a majority of illness related to coronary atherosclerosis [52]. Coronary stents are expandable tubes of metallic mesh placed via percutaneous coronary intervention in order to maintain the patency of vascular lumen. A more comprehensive history of intracardiac stents can be found elsewhere [26••].

Stents are typically made from 316L stainless steel or cobalt-chromium alloys. Adverse effects following stent placement such as persistent chest pain [53, 54] and in-stent restenosis (ISR) have been reported in patients who are allergic to nickel, molybdenum, and gold [55•, 56]. For a more exhaustive list of the adverse allergic reactions reported after stent placement, refer to Honari et al. [26].

In the past, gold was used as a stent coating due to its perceived inert nature. Unfortunately, gold is an active allergen, which has been shown to cause ISR in gold-allergic patients. A 2009 study by Svedman et al. found a correlation between gold allergy and restenosis of gold-plated stents (OR 2.3, $p = .04$) [55•]. Gold is no longer used as a stent coating.

The proposed mechanism of ISR in bare metal stents (BMSs) is through free metal ions acting as haptens, with subsequent recruitment of cytokines and trigger excessive smooth muscle cell proliferation, causing vessel reocclusion. Despite this, it remains unclear whether or not allergy to stent materials is a risk factor for ISR, which has an incidence traditionally reported as between 10 and 30 %. A series of studies in the early 2000s suggested an unclear correlation between metal allergy and ISR [56–61]. However, small patient cohorts and minimal guidance on appropriate testing limited these studies. Thyssen et al. posited no relationship between ISR and metal allergy in their cohort [62]; however, a 2012 study showed that nickel-allergic patients treated with cobalt chromium stents had a significantly increased incidence of ISR compared to the control group [26••]. A 2013 meta-analysis by Gong et al. which included nine studies ($n = 1223$), compared outcomes of patients with and without metal allergy following stent implantation. They found a significant increase in ISR in allergic patients compared to non-allergic patients, OR of 2.65 (95 % CI 1.82–3.82). A subgroup analysis based on race found that the OR in Asians was higher than that in Europeans, suggesting that metal allergies may increase the risk of ISR in certain populations. Nevertheless, the authors encourage the need for prospective clinical trials to determine whether there exists a causal relationship [63••].

Though BMSs were introduced first, drug eluting stents (DESs), which locally release chemotherapeutic agents, are now used in the majority of percutaneous coronary intervention (PCI). This followed a series of studies that

showed a much higher rate of ISR with BMS as compared to DES [64]. By 2004, 80 % of PCIs used DES. Stents can be characterized by their mechanism (self expanding or balloon expanded), metallic composition (stainless steel, cobalt alloy, tantalum, nitinol, gold coating, or biodegradable), or their design (mesh structure, coil, slotted tube, ring, or custom design) [26••].

Historically, stenosis due to metal allergy had not been reported with DESs given their release of immunomodulating agents. However, by 2004, there were 262 reported cases of hypersensitivity symptoms after placement of sirolimus or paclitaxel stents [65]. Newer generations of DES use everolimus and zotarolimus, new polymer coatings aiming to prevent thrombosis. Nevertheless, recent literature suggests that the immunosuppressive qualities of these agents leads to delayed arterial healing and hypersensitivity from foreign body reactions in stent materials. This localized oxidative stress is postulated to cause an increased risk of thrombosis and possibly even contribute to the phenomenon of late restenosis [66]. The immunologic mechanisms of hypersensitivity in DES continue to evolve.

Pacemakers and ICDs

Reported reactions to pacemakers and implantable cardiac defibrillators (ICDs) consist of localized dermatitis, erythema, or pruritus [67, 68]. Non-allergic reactions to these devices include an unidentified sepsis-like syndrome, reticular telangiectatic erythema, and less commonly device failure [69, 70].

Pacemakers and ICDs consist of a generator covered by titanium and leads that attach through the header, which are combined of polymethyl methacrylate (PMMA) and silicone rubber. Conductor wires are made of MP35N, made from alloys of nickel, cobalt, chromium, and molybdenum. The pacing electrodes are made of platinum, platinum-iridium, or platinum-coated tantalum. Albeit rare, titanium is the most common causal agent of pacemaker-induced dermatitis, while nickel, cobalt, chromium, and mercury are less frequent offenders [26••, 71, 72]. An extensive literature review of local and systemic reactions to pacemakers can be found elsewhere [26••]. The differential diagnosis for postimplantation complications is varied; however, it is crucial to rule out infection before suspecting allergy. Use of a polytetrafluoroethylene (PTFE) cover around the device shell often resolves dermatitis. PTFE usage is associated with a slightly increased infection rate, thus keeping its use a second line option [73, 74]. Given the metallic composition of pacemakers, all components must be considered when evaluating MHR following implantation. Treatment of pacemaker dermatitis includes topical corticosteroids, replacement of device with non-causal metals, oral immunosuppression, and use of a PTFE pocket [26••].

PFO/ASD occluders

Allergic reactions to patent foramen ovale (PFO) and atrial septal defect (ASD) occluders are uncommon. The most commonly used device is the Amplatzer occluder (AGA Medical Corporation, Plymouth, MN), made of nitinol, a nickel-titanium alloy. Nickel allergy may be the cause of systemic reactions such as chest discomfort, palpitations, and migraine [53], as well as local reactions confirmed by patch testing [75–77]. Symptoms are reported to resolve following removal of the device or in some cases with corticosteroid treatment. In

2013, a case report described a patient with severe progressive generalized exanthema following implantation of Amplatzer for PFO. This was the first documented case demonstrating confirmed titanium allergy with relation to Amplatzer occluder. Symptoms disappeared immediately after surgical removal [78]. Given the increasing concern over reactions to the Amplatzer occluder, there is a growing effort to identify other options in nickel-allergic patients. In 2009, Reddy et al. assessed outcomes in nickel-allergic patients treated with GORE Helex device, a nitinol wire covered with expanded PTFE. Patients with positive patch tests to nickel underwent successful closure with Helex, and none of them developed allergic reaction, significant chest pain, or arrhythmia. Helex was a safer method of PFO occlusion in nickel-allergic patients ($P < .001$) in this cohort [79]. Cammalleri et al. described the use of Atriasept II (Cardiac Egan, Minnesota, USA), a device containing less metallic material, in patients with nickel allergy and reported no allergic manifestations or complications in those undergoing the procedure [80]. Both studies exhibit an evolving effort to identify safer methods of PFO and ASD occlusion in the nickel-allergic patient population. The authors believe that nickel allergy history should be obtained from all patients prior to placement of an Amplatzer device, and that results from these tests should inform decisions to find a less allergenic device, if indicated.

Spinal cord stimulators

The spinal cord stimulator (SCS), a device that exerts pulsed electrical signals, is a minimally invasive option for treating chronic neuropathic back pain refractory to medical treatment. Reported MHR to components of this device, specifically polyurethane on the device's lead extensions, are rare. At present, only five cases of cutaneous dermatitis are reported [74, 81]. In 2013, Zeshan et al. published a case series on inflammatory reactions to SCS, one of which reported a cutaneous dermatitis that spread along the device's lead length. Though the dermatitis resolved with topical corticosteroids, the patient experienced wound dehiscence 2 weeks later. Within the case series, histologic examination following device explantation revealed evidence of both type IV hypersensitivity reactions and foreign body reactions with giant cell formation. The authors posited the uncertain role of patch testing in relation to SCS and recommended that histology be done to further delineate the immunogenic response [82].

Nuss bars

Nuss bars are stainless steel or titanium bars inserted into the chest cage in order to correct pectus excavatum. Given the extensive documentation of nickel allergy-induced reaction to the stainless steel device, preoperative patch testing for nickel allergy in all patients is now accepted practice [83]. In fact, a recent retrospective study by Shah et al. showed that the rate of metal allergy to Nuss bars was almost triple the prevalence previously estimated [84]. Prior to operation, the Nuss bar manufacturer offers a metal disk for preoperative testing, though patch test confirmation is preferable to metal disk testing. In 2015, Heitmiller et al. sought to determine the sensitivity of the metal disk allergy in comparison to standard patch testing and found that the metal disk may not be

adequately sensitive to determine nickel allergy prior to Nuss procedure, concluding that patch testing with standard formulations of nickel sulfate is the most sensitive way to diagnose nickel allergy [84, 85]. Historically, those who test positively for nickel allergy are treated instead with titanium bars (which are pricier and more difficult to manipulate intraoperatively). Despite a low incidence of titanium allergy, a 2014 case report described a 17-year-old male with a recorded nickel allergy but a negative test for titanium allergy who underwent treatment with titanium bars. He subsequently developed high fever, pleural effusion, and eosinophilia [85]. His symptoms completely resolved with systemic corticosteroid treatment; however, this report serves as a reminder that titanium usage does not preclude allergic response, an important consideration in postoperative Nuss procedure complications. Preoperative testing for metal allergy is recommended prior to the Nuss procedure. While rare, titanium allergy should be a consideration with postoperative complications.

Orthopedic devices

The US Department of Health and Human Services estimates that by 2030, 11 million Americans will have a total joint replacement (TJR) of either the knee or hip, making these the most common elective surgical procedures in the country [86]. Dating back the 1970s, MHR in orthopedic implants have been described in the literature, with 55 cases summarized in 2011 by Basko and colleagues alone [87•]. Case reports have documented cutaneous reactions such as contact dermatitis, erythema [88], vasculitis [89], and urticaria [90], as well as non-cutaneous reactions such as aseptic joint loosening (AJL), pseudotumor formation, and ALVAL [12].

Orthopedic implants can be made of a variety of metallic elements, with the most common being stainless steel, cobalt-chromium-molybdenum (CoCrMo) alloys, nickel, titanium, vitallium, and vanadium [87•, 91] (see Table 1.)

The combined effects of the innate and adaptive immune systems contribute to AJL, a common complication after arthroplasty and the main indication for surgical revision over the long term (AJL is responsible for >70 % of hip revisions and >44 % of knee revisions) [31]. Despite the association between MHR and AJL, current evidence has failed to establish a direct causal relationship between metal allergy and implant failure. However, it is still apparent that metal allergy is one contributor in the complex and multifactorial pathogenesis of prosthesis failure. Indeed, one systematic review found that the prevalence of metal allergy was approximately 25 % in patients with a well-functioning hip and 60 % among patients with a failed implant (~6× the rate in the general population) [11].

Evaluation of MHR

In the evaluation of MHR, it is essential to identify which patients should be tested and when testing should be performed. Previous studies have reported on MHR testing with relation to surgical outcomes. Granchi et al. conducted a meta-analysis including 22 articles ($n = 3634$), which reported metal sensitization in patients both before and after their implantation. Rates of sensitization were significantly increased in patients with failed implants in comparison to

Table 1. Metals and elements used in medical and surgical implants (adapted from [32])

Implant alloy	Alloy elements	Approximate percentage	Medical/surgical uses
Stainless steel SAE 316L	Iron	40–68	Cardiac/intravascular devices
	Nickel	8.3–35	Orthopedic prostheses
	Chromium	20	Plates, pins, nails, bolts, screws, fixators
	Manganese	2	Surgical clips/staples
	Molybdenum	2–3	
Oxinium	Zirconium	97.5	Orthopedic prostheses
	Niobium	2.5	
Nitinol	Titanium	55	Cardiac/intravascular devices
	Nickel	45	Patent foramen ovale occluders Septal defect occluders Bone anchors and staples Essure contraceptive device Urologic devices Dental implants
Titanium	Titanium	90	Orthopedic prostheses
	Aluminum	5.5–6.5	Plates, pins, nails, bolts, screws, fixators
	Vanadium	3.5–4.5	Pacemaker shells
	Nickel	0.012–0.034	Surgical clips/staples
Titanium-tantalum-niobium	Titanium	53	Orthopedic devices and prostheses
	Niobium	25	
	Tantalum	7	
	Zirconium	5	
Cobalt-chromium-molybdenum steel	Cobalt	60	Cardiac/intravascular devices
	Chromium	27–30	Orthopedic prostheses
	Molybdenum	5–7	Plates, pins, nails, bolts, screws, fixators
	Nickel	<0.5	Surgical clips/staples
	Iron	<0.75	Dental implants and restorations
	Manganese	<1	
	Tungsten	<0.2	
	Aluminum	<0.1	
Vitalium	Titanium	<0.1	
	Cobalt	61	Orthopedic prostheses
	Chromium	32	Plates, pins, nails, bolts, screws, fixators
	Silicon	0.5	
	Manganese	0.5	
	Molybdenum	5.6	

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patients with stable TJRs (OR 2.76 95%CI 1.14–6.70) [92]. Another systematic review echoed these results, finding that patients with poorly functioning arthroplasty had positive postoperative metal allergy when patch tested more frequently than those with well-functioning TJRs, OR 1.7 [93]. These findings suggest the possible benefit of MHR testing in patients with prosthetic implants.

Preimplantation

There is no definitive data to conclude that routine preoperative patch testing for all patients improves outcomes. In emergent settings, evaluation for metal allergy is non-essential, as major life- or limb-saving interventions take precedence. In these situations, surgeons should proceed with the best possible and subjectively least allergenic devices.

In elective situations, the role of testing is more complex. Metal allergy diagnosed prior to implant surgery did not increase the risk of implant failure or revision surgery [94]. Similarly, other studies show that patch testing (PT) could not predict whether a patient would experience a stable or failed TJR [92]. On the contrary, a 2012 chart review found that patients who were PT positive and received an allergen-free implant had no postsurgical hypersensitivity complications ($n = 21$), thus insinuating the beneficial role of preoperative PT [95]. It is unclear whether antecedent metal allergy is a risk factor for peri-implant hypersensitivity or if implantation subsequently causes sensitization. Likely, both processes play a role in symptomatic and failing devices postimplantation. Only those with preexisting hypersensitivity will have preimplant positive testing. In those, avoidance may be beneficial.

While the patient's history of metal reactions is important, they are not clearly predictive of which patients will manifest a metal allergy upon implantation. In one study, 369 women were screened before patch testing with two questions: "Are you sensitive, hypersensitive, or allergic to nickel?" and "Do you get a rash from metal buttons, jewelry, or other metal items that come in direct contact with your skin?" [96]. Screening alone only shows positive predictive values of ~60 % for nickel allergy. While screening does not clearly predict metal reactions, it is essential to listen and act upon patient concerns prior to device implant. In individuals who voice metal allergy preimplant evaluation should be considered. Asymptomatic patients do not need evaluation and routine testing for all patients preimplant is unnecessary.

Postimplantation

In the postimplantation setting, evaluation for MHR is not necessary or indicated for asymptomatic individuals. However, for those with symptomatic or failed implants, evaluation can be considered. First, infection and other non-allergic causes of implant symptoms should be ruled out. In patients suspected to have a cutaneous or systemic reaction following implantation, PT is indicated. Diagnostic criteria for suspected MHR following implant are summarized in Table 2 [23••].

PT, LTT, and peri-implant histopathology may be useful to identify individuals who might improve after replacement of a potentially allergenic device [97]. In a recent study, 81 % of metal patch test positive patients had histology consisting of a lymphocytic infiltrate, type IV fibrotic response, and elevated periprosthetic levels of interferon-gamma. Out of the 20 patients, 11 had

Table 2. Consensus diagnostic criteria for MHR postimplantation (adapted from [23••])**Major**

Skin eruption overlying the metal implant

Positive patch test to a metal used in the implant

Complete recovery following implant removal

Chronic dermatitis beginning weeks to months after metal device implantation (local, regional or systemic)

Minor

Unexplained chronic pain and/or implant failure

Therapy resistant dermatitis

Systemic allergic dermatitis reaction morphology consistent with dermatitis (erythema, induration, papules, vesicles)

Histology consistent with allergic dermatitis (cutaneous or peri-implant)

Positive in vitro test to metals, (e.g., lymphocyte transformation test)

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positive PT and LTT reactions and 9 had positive LTT reactions only. Combining PT, LTT results, and potentially histopathology may be useful in better defining patients who would benefit from device replacement [97]. Positive PT to cobalt and chromium are associated with increased knee arthroplasty revision [94].

The field necessitates well-powered, long-term prospective studies to ensure that testing eventually improves postoperative outcomes.

How to test?

- *Patch testing:* Currently, PT is the most widely accepted method for determining hypersensitivity [23••, 32, 98], but no standardized implant-based commercial panels exist for patients undergoing TJR [99]. In a recent international survey, 83 % of American Contact Dermatitis Society members and 96 % of European Society of Contact Dermatitis members felt that PT was the evaluation of choice for MHR [23••]. The role of the patch test is to recreate the delayed hypersensitivity reaction occurring at the implant site on the skin. Some argue PT is insufficient in orthopedic reactions due to its ability to assess only type IV hypersensitivity and because cutaneous reactions may not be representative of periprosthetic tissue [100]. Others have focused on finding more accurate novel patch tests that utilize metal nanoballs, thereby eliminating components of the patch that result in false positives [101].
- *Lymphocyte transformation test:* There is a growing literature base which highlights the potential benefit of LTT, an in vitro test which cultures mononuclear cells from patient blood, mixes it with specific allergens, and measures cell proliferation indicative of hypersensitivity [93, 102].
- *Intradermal testing:* While this approach seems intellectually promising, there is evidence that intradermal testing is unreliable for evaluation of metal allergy [23••, 103].

What to test?

Some argue that baseline series for PT are appropriate based on a patient's geographical location [23••]. Other experts suggest possible prosthesis series that they believe to be a useful baseline screening for all patients [26••, 104]. The ideal PT series however cannot be generalized because it should be informed by patient history and should target the composition in the biomedical device. The metals in various devices that may serve as allergens are summarized in Table 1. Metal series organized by type of prosthesis, including the recommended concentrations/vehicles, is extensively laid out by Schalock et al. [23••]. Testing series should extend beyond metals and include other allergens in implant systems (e.g., adhesive and/or bone cement components) as well as possible other causes of external allergic contact dermatitis on overlying skin.

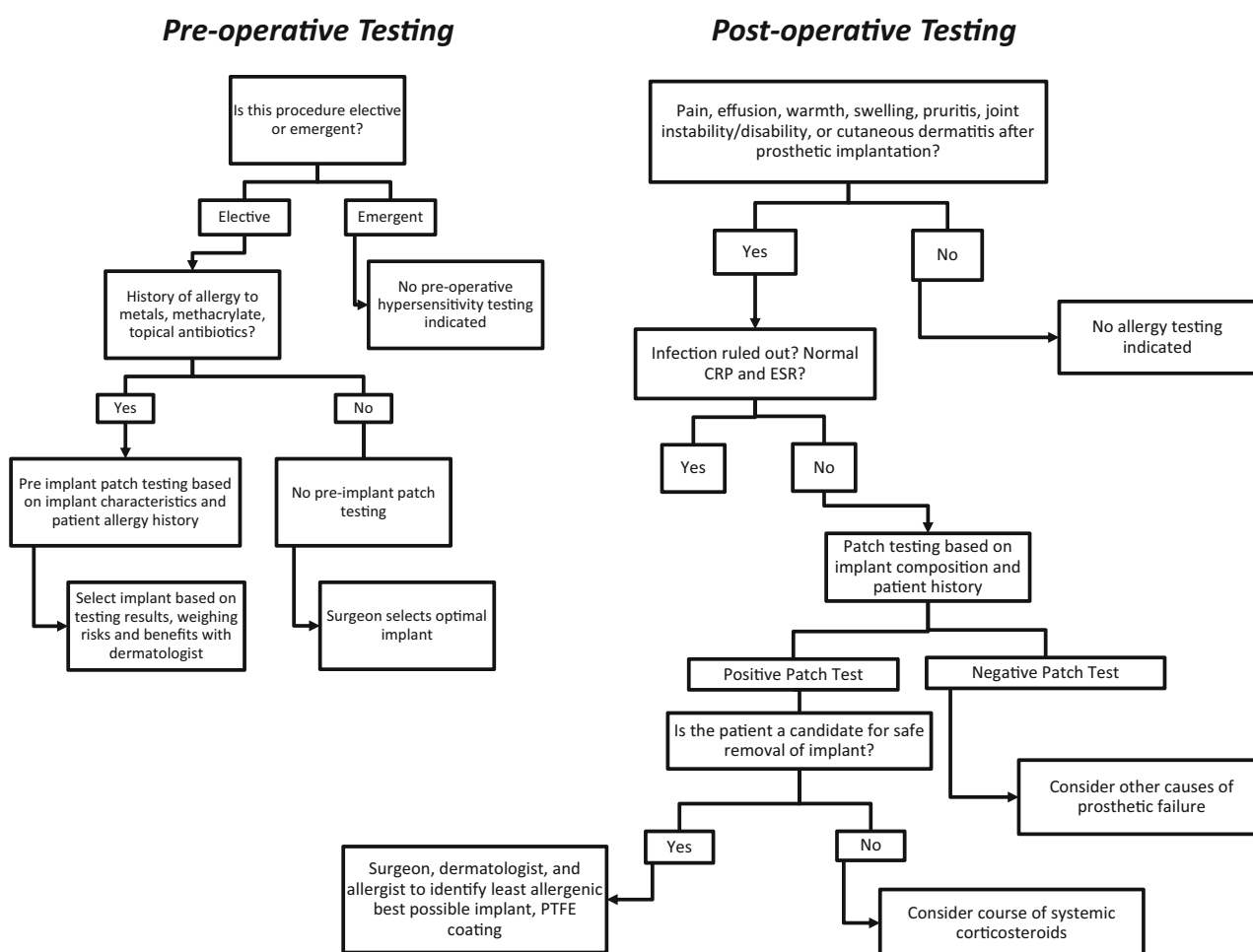


Fig. 1. Guideline to metal allergy testing preoperatively and postoperatively. This is one algorithm to help guide metal allergy testing in the preoperative and postoperative setting.

Bone cement components

Orthopedic implants are often secured with bone cement, which consist of methyl methacrylate, a benzoyl peroxide activator, hydroquinone—a stabilization agent, and gentamicin, an antibiotic, may also be added to bone cements. Numerous studies have reported hypersensitivity reactions to these agents [105, 106]. These reactions are thought to contribute to swelling, cutaneous reactions, AJL, pseudotumor formation, and TJR failure [107]. In one study, 31.8 % of patients with failed arthroplasty were allergic to bone cement components [105]. Bircher et al. found that in patients with failed arthroplasties who patch tested positive to benzoyl peroxide, replacement with bone cement-free implant resulted in complete resolution of symptoms [106]. Bone cement components are an important consideration when evaluating a symptomatic cemented implant.

Management

Choosing the suitable intervention following a positive PT is controversial. A positive PT does not necessitate the presence of symptomatic ACD. In the asymptomatic patient, there is no intervention necessary following positive PT. In symptomatic patients, there is currently no standardized guideline dictating when implant removal is indicated. In symptomatic patients with a positive PT result, it is crucial to consider whether removal of the implant is reasonable and can be accomplished safely without major complications. The patient's dermatologist/allergist and surgeon should discuss the risks and benefits of any proposed intervention. Studies have shown the benefit of replacing the implant with a non-allergenic alloy [75] or alternatively coating the implant with PTFE [26••, 73, 79]. When prosthetic removal is not possible, a 21-day course of systemic corticosteroids may be helpful [15, 108]. A management algorithm was suggested by Schalock et al. [32] and is updated in Fig. 1.

Conclusions

The surgical and medical uses of metal-containing implants are broad and will continue to expand with technologic advances. These metal prostheses greatly improve the quality of life and productivity of patients. Though the literature has an extensive documentation of hypersensitivity reactions to implants, the greater ramifications of these immunologic reactions remains unclear. PT remains the gold standard for diagnosis of ACD, and appropriate testing depends on whether the patient (1) is preoperative or postoperative, (2) has a history of metal allergy, and (3) is symptomatic. Communication between the patient and their medical team remains a key factor to optimizing implant choice and overall patient care. The field still necessitates increased well-powered prospective trials to enhance the role of testing in prevention of complications secondary to metal allergy.

Compliance with ethical standards

Conflict of interest

Lauren N. Ko declares that she has no conflict of interest. Dr. Peter C. Schalock declares that he has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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