

Allergic or Hypersensitivity Reactions to Orthopaedic Implants

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JAAOS Plus Webinar

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Abstract

Allergic or hypersensitivity reactions to orthopaedic implants can pose diagnostic and therapeutic challenges. Although 10% to 15% of the population exhibits cutaneous sensitivity to metals, deep-tissue reactions to metal implants are comparatively rare. Nevertheless, the link between cutaneous sensitivity and clinically relevant deep-tissue reactions is unclear. Most reactions to orthopaedic devices are type IV, or delayed-type hypersensitivity reactions. The most commonly implicated allergens are nickel, cobalt, and chromium; however, reactions to nonmetal compounds, such as polymethyl methacrylate, antibiotic spacers, and suture materials, have also been reported. Symptoms of hypersensitivity to implants are nonspecific and include pain, swelling, stiffness, and localized skin reactions. Following arthroplasty, internal fixation, or implantation of similarly allergenic devices, the persistence or early reappearance of inflammatory symptoms should raise suspicions for hypersensitivity. However, hypersensitivity is a diagnosis of exclusion. Infection, as well as aseptic loosening, particulate synovitis, instability, and other causes of failure must first be eliminated.

Hypersensitivity reactions to implants are uncommon but are reported across orthopaedic, gynecologic, otolaryngologic, cardiothoracic, neurosurgical, and dentistry fields.¹ Plates, screws, wires, pins, sutures, staples, stents, and dental fillings have all been implicated.²

In orthopaedics, allergic or hypersensitivity reactions to metals and other components of implants pose both diagnostic and therapeutic challenges. By far, the best studied and most frequent hypersensitivity reactions occur with metal-on-metal (MoM) hip arthroplasty and hip resurfacing. This topic, which has generated intense controversy, was thoroughly addressed by Bolognesi and Ledford.³ As a complement to their work, this review focuses on hypersensitivities to other large-

joint arthroplasty devices, as well as hypersensitivities to nonmetallic materials such as polymethyl methacrylate (PMMA), implantable antibiotic spacers, polyetheretherketone (PEEK), and a variety of suture, clamp, and staple materials.

It cannot be overstated that hypersensitivity reactions are a diagnosis of exclusion. In arthroplasty patients especially, practitioners must confidently eliminate the more common and often more morbid differential diagnoses of infection, instability, catastrophic wear, and/or fracture before considering metal hypersensitivity.

Most hypersensitivities to both metallic and nonmetallic orthopaedic implants are type IV/delayed-type hypersensitivity (DTH) reactions. Management of implant hypersensitivities should be addressed on an

Table 1

Risk Factors for Cutaneous Metal Hypersensitivity	
Risk Factor	Relative Risk
Female sex	4
Piercings (ears)	3.2
History of hand eczema	3
Metal allergy in first-degree relative	2.8
History of smoking	1.4–3
Following well-functioning arthroplasty	2–3
Following failed arthroplasty	3–6

individual basis because general guidelines do not exist. Although there is no consensus on skin or blood testing for an allergic diagnosis, providers should, at a minimum, inquire about past cutaneous metal reactions, past eczematous skin reactions, and other allergen triggers. Discussion of hypersensitivity reactions and their sequelae should be a routine part of preoperative informed consent.

Epidemiology and Risk Factors

From 10% to 15% of the population exhibits cutaneous sensitivity to metal.² Environmental exposures, inexpensive jewelry, dental fillings, and ingestion of metals (ie, typically zinc and cobalt in dietary supplements) are often implicated.⁴ Nickel is by far the most commonly identified metal allergen; dermal sensitivity to nickel is reported in approximately 14% of the population.² The next most frequently reported allergens are cobalt followed by chromium.² Titanium, vanadium, tantalum, oxidized zirconium, and alumina are considered relatively biologically inert; however, isolated reports of titanium, tantalum, and vanadium allergies have been published.^{5,6} Select risk factors for cutaneous metal hypersensitivity are listed in Table 1.⁷

Females are four times as likely as males to have contact dermatitis to nickel.⁸ This difference is not attributable to a sex-linked genetic or hormonal process but rather to the fact that females across many cultures wear more jewelry, especially piercings, than men do.⁹ This also emphasizes that repeated exposure to an allergen increases the odds for the development of a corresponding allergy. Rates of sensitization are also dose dependent.² For example, the prevalence of metal hypersensitivity is increased in certain occupations, including metalwork, bricklaying, and pottery.⁴

Genetics may also play a role. Having a first-degree relative with hypersensitivity to nickel increases the relative risk 2.8-fold.⁹ Patients with a history of atopic dermatitis (ie, eczema) are highly susceptible to cutaneous metal reactions.¹⁰ Recently, mutations in the filaggrin gene complex, an epidermis-expressed protein involved in skin barrier function, were associated with both nickel allergy and atopic dermatitis.¹⁰

Previous implantation of arthroplasty devices may increase hypersensitivity. Patients with well-functioning and asymptomatic joint prostheses were three times as likely as those without artificial joints to have cutaneous metal hypersensitivity. Hypersensitivity rates were up to six-fold greater in patients with loose or

unstable prostheses than in those with no prostheses.^{9,11}

The temporal relationship between metal hypersensitivity and arthroplasty failure is disputed. Authors are divided on whether metal sensitization occurs after failure of arthroplasty components and excessive particulate wear or whether hypersensitivity reactions to normal wear and ion dissolution cause aberrant inflammatory reactions that result in loosening and failure of the prostheses.²

Pathophysiology of Hypersensitivity Reactions

Hypersensitivity reactions are a function of the adaptive immune system. They involve either B-cell (ie, antibody-producing) lymphocytes or T-cell (ie, antigen-processing, -presenting, and -killing) lymphocytes. Adaptive immunity reactions must be distinguished from innate immunity reactions in which monocytes, macrophages, and giant cells, among others, instinctively attack certain bacteria, viruses, and other foreign materials, such as polyethylene debris. The latter, albeit similar to a reaction to metal-induced failure, is not generally considered a true hypersensitivity reaction; rather, it is a normal reaction to abundant foreign material.

The confusion is understandable; some authors have been criticized for loosely using the terms implant allergy and metal allergy to describe any device that “[aseptically] fails prematurely (<7 years) due to an exuberant cell-mediated immune response to the same amount of implant debris that is typically well tolerated by most people.”⁶ Indiscriminate use of the term hypersensitivity to refer to all inexplicable failures is akin to declaring a penicillin allergy in every patient who experiences antibiotic-related nausea or gastrointestinal tract upset. True

Table 2**Mechanism of Action, Cellular Mediators, and Reaction Time by Type of Hypersensitivity Reaction**

Type	Cellular Mediator	Pathophysiologic Characteristics	Typical Reaction Time	Clinical Examples
I	B cell	IgE antibodies cause mast cell degranulation	10–30 min	Seasonal, food, and latex
II	B cell	IgG/IgM antibodies cause cytotoxic destruction	Variable (minutes to hours)	ABO blood type incompatibility, myasthenia gravis, Graves disease
III	B cell	IgG/IgM antibodies cause immunocomplex deposition	3–8 hr	Rheumatoid arthritis, SLE
IV	T cell	T cell (not antibody) mediated	12–72 hr	Contact dermatitis, chronic transplant rejection, MS

Ig = immunoglobulin, MS = multiple sclerosis, SLE = systemic lupus erythematosus

hypersensitivity reactions are pathophysiologic disease processes classified by their distinct mechanisms of action. Table 2 describes hypersensitivity reactions according to their mechanisms, mediators, and speed of onset.

Type I reactions are the most common and widely recognized hypersensitivities. Type I reactions occur rapidly, within minutes of exposure. They are mediated by preformed circulating immunoglobulin (Ig) E antibodies that bind to an allergen on contact, triggering mast cell degranulation and histamine release. Histamine causes regional inflammation, edema, and vasodilation. Symptoms range from mild itching to potentially lethal anaphylaxis. In severe cases, systemic hypotension may result, otherwise known as anaphylactic shock. Type I hypersensitivities include seasonal and food allergies, asthma, and latex allergies. Type I reactions to orthopaedic implants are rare, but the development of IgE antibodies against protein-metal complexes of nickel, cobalt, and chromium have been reported.^{9,12} Nickel ions are thought to trigger mast cell degranulation by a nonimmunologic or atypical immunologic mechanism.¹²

Type II hypersensitivity reactions are the mechanism behind many drug allergies and autoimmune diseases. In type II autoimmune diseases, IgM and IgG antibodies show affinity to anti-

gens on various cells, leading to the immunological perception that some native tissues are foreign. Related conditions include the development of antibodies to acetylcholine receptors in myasthenia gravis, a neuromuscular disease, and antibodies that bind to and stimulate thyroid receptors in Graves disease. Other type II reactions include hemolytic reactions to incompatible blood types.

Like type II hypersensitivities, type III hypersensitivities involve antibodies that develop an affinity for native tissues. However, instead of attacking tissues locally, antibody-ensnared native antigens circulate freely until they eventually deposit in various distant locations, such as the synovial joints or kidneys. Following deposition, an inflammatory response eventually causes collateral destruction of surrounding tissues, such as the synovium in rheumatoid arthritis or the renal glomeruli in systemic lupus erythematosus. Note, however, that some spondyloarthropathies (ie, ankylosing spondylitis, psoriatic arthritis, reactive or Reiter arthritis) are not considered antibody-mediated processes, hence their designation as seronegative arthropathies.

Type IV hypersensitivities differ from types I to III in that they are mediated not by B cell–derived antibodies but by T cells, a class of lymphocytes that detect, process, and attack various

antigens. Type IV hypersensitivity reactions are also termed DTH because cell-mediated reactions take longer to initiate than those triggered by antibodies. Type IV, or DTH, reactions occur at a minimum of 12 hours after exposure and usually peak at approximately 72 hours.⁹ Common examples of DTH include contact dermatitis from poison ivy or nickel, as well as chronic rejection of transplanted organs, reactions to tuberculin skin tests, and multiple sclerosis.

Most hypersensitivities to both metallic and nonmetallic orthopaedic implants are type IV/DTH reactions. In this type of deep-tissue DTH reaction, metallic particles are generated by corrosion, abrasion, and/or dissolution of the implant. The ionized particles bind with native proteins, and the formed complexes are recognized by histiocytes as well as other antigen-presenting cells that phagocytize, process, and present antigens to T cells.¹³ Between the T-cell lymphocytes and macrophages, a surge of proinflammatory factors are released, including interleukin (IL)-1, IL-2, and IL-6; interferon- γ ; tumor necrosis factor; and receptor activator of nuclear factor- κ B ligand.⁶ These factors promote osteoclast activity and inhibit osteoblast activity, leading to localized osteopenia, osteolysis, and potential catastrophic loosening.¹⁴

Clinical Presentation

Patients with hypersensitivity to an implant typically have prolonged eczematous dermatitis that is localized to the region overlying the device. Patients often have persistent postoperative pain and swelling.^{1,3} Although pruritic and erythematous rashes may regionalize to the skin overlying an implant, they may not concentrate at the incisional margins, as is often observed with a postoperative infection. Inflammation is usually regional, but disseminated variations have been reported.⁴

It cannot be overstated that hypersensitivity reactions are a diagnosis of exclusion. In arthroplasty patients especially, practitioners must confidently eliminate the more common and often more morbid differential diagnoses of infection, instability, catastrophic wear, and/or fracture before considering metal hypersensitivity.³

Additional Studies

Imaging

Radiographic findings are nonspecific for hypersensitivity reactions, but imaging may help eliminate many of the aforementioned differential diagnoses. Plain radiographs should be used to rule out component malpositioning, fractures, or other types of catastrophic failure. Plain radiographs, as well as CT and/or bone scintigraphy, may demonstrate periprosthetic osteolysis that is suggestive of, but by no means specific for, hypersensitivity reactions. Recent attention has focused on the role of metal artifact reduction sequence MRI in the evaluation of aseptic lymphocytic vasculitis-associated lesions (ALVALs) and pseudotumor; however, the technique is not yet standardized.³ Metal artifact reduction sequence MRI reduces distortion from metallic implants and allows

better visualization of the periprosthetic soft tissues than CT does.¹⁵ MRI is also effective for diagnosing other sources of pain, such as iliopsoas tendinitis, trochanteric bursitis, nerve irritation, and other lumbosacral or pelvic pathology.¹⁶

Ultrasonography has been a reliable screening tool for ALVALs around total hip prostheses.^{16,17} In a recent comparison of ultrasonography with MRI for the detection of ALVAL hip lesions, there were no substantial differences in the diagnostic sensitivity or specificity of these modalities. Proponents of ultrasonography argue that the technology has several key advantages over MRI, including comparatively lower costs, superior ease of access, minimal (if any) contraindications, and nonsusceptibility to metallic-artifact distortion.¹⁸

Laboratory Studies

Initial laboratory studies serve primarily to rule out infection. At a minimum, a complete blood cell count with manual differential, erythrocyte sedimentation rate, and C-reactive protein level should be obtained.³ When a metal hypersensitivity reaction is occurring, serum inflammatory marker levels can range from normal to mildly elevated.³

The role of serum metal ion levels in diagnosing an allergic reaction to orthopaedic implants is the subject of ongoing investigation. Several studies suggest that elevated ion concentrations are associated with early failure in MoM hip arthroplasty bearings. Metal ion testing should be conducted in patients with symptomatic MoM implants or those with radiographic changes.³ Pending positive imaging results, elevated serum ion levels (>5 ppb [or mg/L]) typically indicate the need for advanced imaging and joint aspiration.^{3,19} Some authors advocate baseline and periodic serum ion screenings even in

low-risk asymptomatic patients (ie, those with well-positioned components with acceptable track records and without evidence of radiographic osteolysis).¹⁶

As noted, joint aspiration is performed when clinically warranted or when laboratory values are inexplicably abnormal. Cytology may reveal elevated white blood cell counts, particularly an elevated percentage of monocytes.³ However, such findings are not specific for hypersensitivity reactions, and neither current guidelines nor widely accepted cutoff ranges exist. Some authors advocate manual cell counts because metallosis may distort automated quantification.³ There is no demonstrated utility in testing aspirated fluid for metal ion concentrations.²⁰

Allergy Testing

Three major types of allergy tests are available. Epicutaneous patch testing is considered the benchmark for atopic dermatitis in the dermatology community.^{4,21} However, its accuracy is strongly observer dependent, and results may vary on the basis of the dermal region tested, environmental factors, contaminants, non-standardized sample concentrations, and a variety of other host-related factors.²² Furthermore, the antigen-presenting cells of the skin (ie, Langerhans cells) are exclusive to the dermis and process antigens with a mechanism substantially different from that of deep-tissue macrophages.^{2,9} These issues limit the reliability of preoperative patch testing for identifying potential implant hypersensitivity.

Alternatively, oral metal challenges are limited by many of the same subjective variables as skin testing. Testing more than a single agent at once is also difficult.²³ In addition, oral metal challenges have not been closely investigated in the orthopaedic literature.

Finally, lymphocyte transformation testing (LTT) reacts with lymphocytes isolated from a peripheral blood draw with a variety of antigens, including nickel, cobalt, chromium, molybdenum, vanadium, and zirconium.²⁴ Proponents argue that LTT better represents the conditions of the periprosthetic milieu.⁶ LTT is also thought to be more sensitive than skin patch testing, but this has not been clearly demonstrated in the orthopaedic literature.⁶

Currently, there is considerable debate regarding whether allergy testing is necessary before routine arthroplasty. Most surgeons agree that when patient history is negative for cutaneous hypersensitivity, routine implantation may proceed.²⁵ However, when patients report metal allergies, experts disagree on the best course of action. In a small study, 22 patients with self-reported cutaneous metal sensitivities underwent skin patch testing, and 83% had positive results.²⁶ These results may suggest that self-reported allergy histories are sufficiently sensitive to proceed directly to implantation with alternative bearings. Another study followed up on 18 patients whose preoperative skin tests were positive for metal allergies but who nonetheless received allergenic arthroplasty components. None was found to have dermatologic or joint-related symptoms at an average of 6.3 years postoperatively.²⁷

The association between skin, oral, and serum metal hypersensitivity and deep-tissue (ie, periprosthetic) hypersensitivity is highly contested. Currently, no test is widely accepted or recommended for the clinical determination of implant hypersensitivity.

Hypersensitivity to Metal Implants

Hip Arthroplasty

Complications from metal hypersensitivity are reported more frequently

in MoM total hip arthroplasties and hip resurfacings than with any other orthopaedic procedure. Reactions to MoM hip bearings have been reported since the early 1970s.²⁸ Retrieval studies of first-generation MoM hips in patients with persistently symptomatic aseptic joints revealed a lymphocyte-dominated cellular response.²⁹ Most patients had persistent preoperative pain or early recurrence of pain after the index arthroplasty. Inflammatory markers were notably negative, but radiographs demonstrated the development of substantial periarticular osteolysis.

Ultimately, first-generation implants were abandoned for lower-friction materials, such as the Charnley metal-on-polyethylene (MoP) design; however, the concept of MoM bearings was not abandoned entirely. In the 1980s, a second generation of MoM hip implants improved on the mechanical shortcomings of their predecessors. They featured longer stems, decreased frictional torque, improved clearance (polar bearings over equatorial bearings), and smoother surface finishing.²⁶ Second-generation MoM hips also exhibited less volumetric and linear wear. However, because of the exceedingly small size of metal particles produced, next-generation MoM bearings actually generated a greater number of individual particles than first-generation models did. The smaller size (0.05- μ m diameter) facilitated particulate diffusion into surrounding tissues. Metal deposits in second-generation implants have also been found at distant sites, such as regional lymph nodes and the liver and spleen.¹⁴

Histologic evaluation of periprosthetic tissues of patients who had revisions of MoM hip arthroplasties demonstrated cell-mediated type IV hypersensitivity/DTH reactions, which are characterized by accumulations of periarticular monoclonal or oligoclonal T cells in addition to monocytes and macrophages. The characteristic

aggregates, perivascular lymphocytes and chronic inflammation, are known as ALVALs. An ALVAL refers to the same disease entity as an adverse local tissue response, metal hypersensitivity reaction, adverse reaction to metal debris, and pseudotumor—the last of which refers to a periarticular cystic inflammatory mass with histologic features identical to those of the other tissue responses.^{3,11,30,31}

Despite the recent spotlight on second-generation MoM bearings, metal hypersensitivity reactions have occurred in other scenarios, including joint arthroplasties with MoP bearings. Several recent studies describe high rates of early ALVAL-related failures in modular total hip systems, with fretting and corrosion occurring at the neck-stem junction.^{29,32}

Metal hypersensitivity reactions may also occur when manufacturers and sizes of hip prosthetics are mixed and matched. In retrieval studies of mixed-component constructs, investigators noted intact bearing surfaces but substantial trunnion wear at imperfectly fitting junctions. Substantial trunnion wear, or trunnionosis, has been associated with ALVAL and pseudotumor formation even in the setting of MoP bearings.^{30,33} The finding that the imperfectly fitted trunnions were not caused by hypersensitivity may support the argument that metal hypersensitivity is the result of excessive particulate generation and not vice versa.

Other Large-joint Arthroplasty

DTH reactions are considerably less common with prosthetic knee components than with hip components; however, the symptoms may be more prominent because of the superficial anatomy of the knee. In a mechanism similar to trunnionosis, ALVAL has been reported in revision knee prostheses that use Morse taper modular connections.³⁴ Not unexpectedly,

Table 3**Elemental Composition and Comparative Biological Reactivity of Common Orthopaedic Metals**

Orthopaedic Metal	Relative Immunogenicity	Elemental Composition								
		Ni	Co	Cr	Mo	Ti	Al	Va	Fe	Other
Stainless steel 316L	High	8%–35%	—	20%	2%–3%	—	—	—	>50%+	2% manganese, up to 1% silicone
Co-Cr-Mo	Moderate	0%–0.5%	60%–70%+	27%–30%	5%–7%	—	—	—	—	Up to 1% manganese and silicone
Vitallium	Low	—	61%	32%	5.6%	—	—	—	—	<0.5% manganese and silicone
Titanium alloy	Low	—	—	—	0%–15%	85%–99%+	0%–6%	0%–4%	—	—
Oxinium	Very low	—	—	—	—	—	—	—	—	97.5% zirconium and 2.5% niobium
Nitinol	High	45%	—	—	—	55%	—	—	—	—

Al = aluminum, Co = cobalt, Cr = chromium, Fe = iron, Mo = molybdenum, Ni = nickel, Ti = titanium, Va = vanadium
 + Indicates remaining balance; — indicates nil but may contain a trace (<0.01% composition by weight)

these hypersensitivity reactions have been associated with a substantial decrease in patient satisfaction and loss of function.³¹

DTH reactions have also been reported following implantation of intervertebral disk replacements. A case series of one cervical and three lumbar MoM devices exhibited initially positive outcomes but with early return of axial and/or radicular symptomatology. On exploration of the lumbar MoM devices, surgeons encountered “a thick, yellowish, avascular soft-tissue mass [that was] responsible for an epidural-mass effect on the thecal sac.”²⁴ Histologic evaluation in all cases demonstrated lymphocyte-predominant DTH reactions with an appearance similar to that of MoM hip hypersensitivity reactions. In all but one case, removal of the device resulted in complete resolution of symptoms.

Internal Fixation

The elemental composition of commonly implanted orthopaedic metals is listed in Table 3. Hypersensitivity

reactions to internal fixation devices are markedly less common than reactions to arthroplasty devices. This is probably because fracture and osteotomy stabilizing devices have no macroscopically moving bearings and because once bony union occurs, the devices undergo relatively little motion. A small prospective study evaluated patients undergoing internal fixation with stainless steel implants after preoperative cutaneous metal tests. No substantial complications were observed at 2-year follow-up, despite 6% of patients having positive test results for nickel allergies.³⁵ In a similar but retrospective report, a relatively low incidence of positive cutaneous reactions to metal (19 of 1,600 patients, or 1.2%) was found in patients with stainless steel plates, screws, wires, pins, and staples.³⁶ Animal models suggest there is no difference in the strength of screw fixation in subjects known to be sensitive to nickel, cobalt, or chromium and in those who were not.⁹

As with joint arthroplasties, mere implantation of internal fixation

devices may sensitize patients to metals. A prospective study of metal allergy—negative patients who underwent internal fixation with stainless steel devices demonstrated postoperative nickel, cobalt, and chromium sensitization at rates of 3.8%, 3.8%, and 2.7%, respectively.³⁶ Rates of desensitization were similar, with 2.1% of initially nickel-sensitive patients and 3.8% of initially cobalt-sensitive patients having negative results for respective dermal hypersensitivities at 6 months postoperatively.³⁷

Clips, Staples, and Other Devices

Vascular clamps, anastomotic staples, and other types of clips are manufactured from stainless steel, titanium, cobalt-chromium, tantalum, and other organic polymers. Titanium clips are often preferred because they are relatively inert, nonferromagnetic, and inexpensive.

Most skin staples available today are made from stainless steel (ie, predominantly iron, nickel, and chromium), but spectrometric analyses

of 18 brands of suture clips indicated that many of these devices contain not-insignificant quantities of cobalt, molybdenum, and titanium.³⁷ Although the temporary nature of severe dermal nickel reactions rarely causes problems, some authors associate these reactions with delays in wound healing.³⁸ Severe reactions to staples may be indicative of a preexisting metal hypersensitivity and should prompt close monitoring of underlying implants, especially MoM devices.⁹

Hypersensitivity to Nonmetallic Implants

Polymethyl Methacrylate

Hypersensitivities to a variety of nonmetal materials have been described. Reports of allergies to *N,N*-dimethylparatoluidine, an accelerator used in certain types of bone cement, are also relatively frequent. In the field of dentistry, where *N,N*-dimethylparatoluidine (ie, along with cobalt and chromium) has been associated with allergic contact stomatitis, type IV/DTH reactions are well recognized.³⁸ Other cement additives implicated in hypersensitivity reactions are benzoyl peroxide and hydroquinone.³⁹

Perhaps the most commonly implicated nonmetal allergen is PMMA. In an analysis of 26 patients with aseptic loosening of cemented hip prostheses, 50% of patients with loose prostheses had positive patch test results for PMMA versus zero positive patch tests in those with well-fixed devices.⁴⁰ Hypersensitivity to cement is more commonly reported when it is mixed with antibiotics, gentamycin being the most commonly implicated additive.^{1,39}

Polyetheretherketone

PEEK is often lauded for its biologic inertness; however, at least one recent

report detailed PEEK hypersensitivity after its implantation as an intervertebral cervical spacer. After extensive workup, the skin test result was positive for PEEK in the setting of an otherwise negative spectrum of common allergens. Removal of the device resulted in a rapid resolution of symptoms.⁴¹ Overall, PEEK hypersensitivities are remarkably rare.

Bioabsorbable Implants

Bioabsorbable sutures and implants, such as screw, rods, and anchors, are typically manufactured from polyglycolic acid and polylactic acid polymers. In a large retrospective study of more than 2,500 patients who received such implants, 4.3% experienced inflammatory, sterile tissue reactions.⁴² Polyglycolic acid implants were substantially more likely to cause inflammatory reactions than were polylactic acid implants (107 of 2,037 patients [5.3%] versus 1 of 491 patients [0.2%], respectively). Extensive radiographic osteolysis and chronically draining aseptic wounds were observed in severely affected patients.

Suture Materials

Reactions to suture materials vary considerably by suture composition. Although reactions to nonabsorbable materials, such as synthetic nylon and polypropylene, are rare, reactions to biologically foreign proteins, such as silk and catgut, can be robust.⁴³ Tissue reactivity generally increases with suture thickness and with multifilamentous varieties compared with monofilamentous varieties.

Absorbable sutures require a host cellular reaction to dissolve. In most cases, these are innate foreign body reactions and not true hypersensitivity reactions; however, the latter is possible. Animal gut-derived sutures can trigger rapid-onset type I IgE-mediated allergies.⁴⁴ Both foreign proteins and chromium salts in chromic gut sutures

can cause type IV/DTH reactions, as can the fibrous proteins of natural silk.⁴⁴ Additionally, a variety of suture products contain the antibacterial additive triclosan, which may itself trigger contact dermatitis.⁴⁴

Hypersensitivity reactions to high-tensile strength orthopaedic sutures, such as FiberWire (Arthrex) and Ti-Cron (Tyco), have been linked to clinical failure.⁴⁵ High-tensile suture compositions include polyester, polyethylene, and/or polypropylene. In animal model testing, immunogenicity of eight leading brands found no substantial differences in histologically graded inflammation.

Finally, reports of DTH hypersensitivities to 2-octyl cyanoacrylate are emerging in the literature.⁴⁶ One surgeon reported on a series of rash-like symptoms in 15 of 912 total knee arthroplasty procedures closed with 2-octyl cyanoacrylate; however, formal allergy testing was not performed.⁴⁷ For acutely symptomatic patients, authors recommend immediate removal of adhesive using acetone or petroleum jelly or by rubbing the adhesive with gauze pads.⁴⁷

Management of the Symptomatic Implant

Management of implant hypersensitivities should be addressed on an individual basis because general guidelines do not exist. One major exception, however, is a recent consensus statement on the risk-stratified management of MoM hip arthroplasties issued by the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, and The Hip Society.⁴⁸ Optimal management of MoM total hip arthroplasty depends on a variety of factors including, but not limited to, symptom severity, radiographic osteolysis, circulating metal ion levels, implant positioning, and the track record of the

manufactured implant.³ Authors of the consensus statement indicated that low-risk patients—those with well-fixed, track-proven implants and no symptoms—may be followed up annually. Moderate risk patients—those with well-fixed, well-positioned components but who exhibit some symptomatology and/or have manufacturer-recalled implants—should be followed more closely (ie, every 3 to 6 months).^{3,16} Revision surgery should be considered in patients with moderate risk and progressive symptomatology, imaging abnormalities, or rising ion levels. For high-risk patients—those who are severely symptomatic, have high ion levels (>10 ppb), and/or substantially malpositioned components—revision is generally recommended.³

Revision strategies vary depending on the integrity of the hip capsule, the presence of intracapsular or extracapsular effusion, and the functionality of the abductors.³ Generally speaking, in a patient with an intact capsule and contained intracapsular effusion, stability is less concerning, and thus only the bearing and/or cup must be revised. The presence of extracapsular effusion, however, is suggestive of instability; in these situations, surgeons should have a low threshold for revision of all components. Frank involvement of the abductors is strongly suggestive of instability and should be treated with constrained liners or other salvage measures. Bearing surfaces may be converted to MoP or ceramic-on-polyethylene articulations. At this time, either combination is an acceptable solution for ALVALs.³

Metal hypersensitivity in total knee arthroplasty is a less-common and less-studied condition. Most authors describe conversion of the offending cobalt-chromium implants to zirconium femoral implants paired with either titanium tibial trays and polyethylene spacers or all-polyethylene monoblock tibial implants. Nitride-

coated titanium femoral implants have also been used.⁴⁹ In the rare instance of titanium allergy, some authors reported success with customized Oxinium (Smith & Nephew) implants.⁵ These implants are hypoallergenic, consisting of a metal/ceramic composite (97.5% zirconium and 2.5% niobium) with an oxidized zirconium surface coating.⁵ Ceramic knee components are available with and without polyethylene spacers, allowing surgeons to potentially eliminate metal altogether.

For internal fixation, titanium implants are readily available first-line alternatives to most stainless steel and cobalt-chromium systems.⁵ Although some authors reported symptom management with topical steroid and/or systemic steroids, evidence is insufficient to recommend this technique.⁶ In addition, steroids may lead to delayed healing, wound breakdown, and immunocompromise. Relatively little evidence is available on the safety or efficacy of atropine sulfate, anti-inflammatory medications, and antihistamines for symptomatic hypersensitivity management; no such treatments can be recommended at this time.^{2,5}

Summary

Allergies or hypersensitivity reactions to a variety of metal and nonmetal orthopaedic implants may pose diagnostic challenges to the unsuspecting provider. Hypersensitivity symptoms closely mimic infection, aseptic loosening, and other sequelae that must be eliminated before the diagnosis of hypersensitivity can be made. Surgeons must appreciate that true allergic reactions are well-defined pathophysiologic processes and do not simply refer to inexplicable, aseptic, and/or premature failures. Although there is no consensus on skin or blood testing for an allergic

diagnosis, providers should, at a minimum, inquire about past cutaneous metal reactions, past eczematous skin reactions, and other allergen triggers. Discussion of hypersensitivity reactions and their sequelae should be a routine part of preoperative informed consent.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 14, 22, and 23 are level I studies. Reference 19 is a level II study. References 16-18, 20, 21, 29, 33, 34, 36, 37, 42, 46, 47, and 49 are level III studies. References 12, 15, 24, 26-28, 30, 32, 35, 38, 39, 41, and 44 are level IV studies. References 1-11, 13, 25, 31, and 48 are level V expert opinion.

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