Surgical implants have a wide array of therapeutic uses, most commonly in joint replacements, but also in repair of pes cavus and spinal disorders, in cardiac devices (stents, patches, pacers, valves), in gynecological implants, and in dentistry. Many of the metals used are immunologically active, as are the methacrylates and epoxies used in conjunction with several of these devices. Allergic responses to surgical components can present atypically as failure of the device, with nonspecific symptoms of localized pain, swelling, warmth, loosening, instability, itching, or burning; localized rash is infrequent. Identification of the specific metal and cement components used in a particular implant can be difficult, but is crucial to guide testing and interpretation of results. Nickel, cobalt, and chromium remain the most common metals implicated in implant failure due to metal sensitization; methacrylate-based cements are also important contributors. This review will provide a guide on how to assess and interpret the clinical history, identify the components used in surgery, test for sensitization, and provide advice on possible solutions. Data on the pathways of metal-induced immune stimulation are included. In this setting, the allergist, the dermatologist, or both have the potential to significantly improve surgical outcomes and patient care. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:683-95)

Key words: Metal sensitization; Nickel; Cobalt; Chromium; Bone cement; Methacrylates; Patch testing; Joint replacements; Orthopedic implants

ORTHOPEDIC IMPLANTS

Case

Donald Taylor is a 68-year-old man referred by his orthopedic surgeon for an “allergy evaluation.” The patient reports persistent joint pain and swelling that began about 6 weeks after his right total knee replacement was performed 15 months earlier. Joint aspiration performed 3 months ago showed 5000 white blood cells (WBCs), with a differential of 74% lymphocytes, and 26% neutrophils. Cultures held for 2 weeks showed no growth. A complete blood cell count was normal with normal WBC counts, the C-reactive protein level was minimally elevated, but the erythrocyte sedimentation rate was normal. These findings indicate that the patient does not have an infection as the cause of his knee failure. An X-ray of the knee showed good alignment of the implant, with only minor lucency noted along the tibial plate. The alignment and size are noted to be appropriate, suggesting that a mechanical problem is not the cause of the patient’s knee failure. A triple-phase bone scan showed increased uptake in the right knee, slightly more than would be expected after a recent knee implant. The surgeon requests an allergy evaluation to determine whether this may be the cause of the patient’s joint failure. (In this review, the terms “sensitization: and “allergy” will be used interchangeably. Although this is incorrect from an immunological standpoint, these terms are frequently substituted in other specialties, to whom this review may also be useful.)

Differential diagnosis

Joint failure is defined in orthopedic terms as a replaced joint that does not function well. A good deal of research has investigated the causes of joint failure, and, interestingly, the current orthopedic literature does not consider sensitization to implant components as a frequent reason for joint replacement failure. In a review of 781 total knee arthroplasties requiring revision, the most common failure mechanisms that were listed included loosening (40%), infection (27.5%), instability (7.5%), periprosthetic fracture (4.5%), and arthrofibrosis (4.5%).1 Revision for infection occurred early, less than 2 years from implant surgery, and aseptic loosening was the most common cause reported for late revisions.1 Causes of total hip arthroplasty failure, based on 1272 patients (1366 hips) who required revision of their hip implant between 2000 and 2007 from the same institution,2 implicated aseptic loosening (51%), instability (15%), wear (14%), infection (8%), fracture (5%), and miscellaneous (7%).2 Obesity is a known risk factor for poor outcome in both primary hip1 and knee1 replacements. Other risk factors for joint failure include hemarthrosis5 and microbleeding into the joint,6 osteopenia and osteoporosis,7 and cigarette smoking.8,9 Trauma to the joint from replacement surgery can rarely trigger complex regional pain syndrome (ie, reflex sympathetic dystrophy). An expert opinion survey of the members of The Knee Society published in 201310 listed total knee arthroplasty complications and adverse events in order of importance as bleeding, wound complications, thromboembolic disease, neural deficit, vascular injury, medial collateral ligament injury, instability, malalignment, stiffness, deep infection, fracture and dislocation, bearing surface wear, osteolysis, reoperation, revision, and...
death as the most common. Immunologically based inflammation was not on the list.

Yet the inflammation associated with sensitization to 1 or more joint components can plausibly cause a number of these mechanical complications, such as aseptic loosening, instability, stiffness, arthrofibrosis, swelling, warmth, and pain.11,12 This suggests that implant sensitization may underlie a number of implant failure findings that, to date, have not been specifically identified as the cause. This is where the allergist/immunologist can have the most impact—in making the diagnosis of sensitization to implant components as an increasingly recognized and important cause of joint failure that can be treated once the allergens are identified.

Clinical presentation

Part of the difficulty in determining the reason for joint failure is that the clinical presentation is common to a number of causes, which broadly include allergy, infection, and mechanical mismatch and scarring. Symptoms common to all 3 typically consist of joint pain, joint swelling, and warmth.13 Other nonspecific presentations of joint failure may include implant loosening, instability, and osteolysis.14 For example, adverse local tissue reactions to metal-on-metal hip replacements have been reported to arise from corrosion,15 infection,16 and allergy,17 and the clinical symptoms alone are insufficient to determine the cause.12 Metal debris from metal-on-metal hips may cause metallosis and pseudotumor formation from the toxic and necrotic effects of local metal ions,18,20 loosening and instability from local inflammation, and, importantly, metal sensitization. Several articles have attempted to differentiate between joint failure due to infection versus joint failure due to metal sensitization, admitting that the clinical presentation does not serve to distinguish the cause.12,22

Evaluation of synovial fluid may help to establish the reason for the joint failure. A synovial fluid WBC count of more than 12,800 cells/μL, more than 89% polymorphonuclear lymphocytes, elevated C-reactive protein level of more than 95 mg/L, and elevated erythrocyte sedimentation rate have been shown to sensitively and specifically differentiate hip arthroplasty failure from infection23 compared with other causes. A meta-analysis of 15 such studies supported the conclusion that the number of WBCs in synovial fluid coupled with a predominant percentage of polymorphonuclear lymphocytes was sensitive and specific for joint infection, although the thresholds varied from 1100 to 6200 WBC/μL and from 60% to 89% polymorphonuclear lymphocytes.24 In contrast, a different study of 54 patients with knee failure suggested that elevated monocyte and lymphocyte cell counts were possible indicators of wear rates of the tibial polyethylene insert and could differentiate that cause from infection.25 Fluorescence-activated cell sorting analysis of joint fluid from 72 total knee arthroplasties from 64 patients with postoperative joint effusions differentiated metal-sensitized patients by a preponderance of CD3+CD45RO+ T cells compared with an increase in CD14+ macrophages in patients with particle-induced synovitis and increased CD16+ neutrophils in those with deep infection.26

Taken together, most patients with joint replacement failure (of any cause) present with common symptoms of joint pain, swelling, and decreased range of motion. An eczematous dermatitis over the implant site is rare, but more likely to be caused by sensitization to implant components as patients with implant-localized dermatitis have a 47% to 67% incidence of positive patch test results.27 Such patients are more likely to be reported in the dermatological and allergic literature than in orthopedic reports. The lack of cross-talk between these and orthopedic specialties may be the reason that allergy to implant components is, as yet, not commonly considered in the differential diagnosis of joint failure in the orthopedic literature.

Sensitizing components of medical implants

Medical implants are made of a number of allergenic materials that have been separately reported to cause sensitization and contact dermatitis.

Metals used in surgical implants. Patients may be previously exposed to metal through personal products such as jewelry, piercings, braces, watchbands, belt buckles, or jean snaps (Table I). The timing and route of personal exposure appears to help determine the response. Patch testing of 1501 eighth-grade students in Denmark demonstrated that the lowest prevalence (1.7%) of nickel sensitization occurred in those who had dental braces before ear piercing and the highest (20.4%) in those who first had pierced ears and then braces.28 Other exposures causing metal sensitization can occur in the workplace, such as primarily in industrial settings of metal smelting, refining, pouring, machining, electroplating, or direct handling of metals and metal items. Work with metals in the laboratory and research setting can also cause metal sensitization.

Bone cement. Bone cement, a polymethyl methacrylate (PMMA), is used in a number of orthopedic procedures in which it serves as a kind of grout that is squirted under pressure to fill the space between the implant and the bone. Bone cement is almost always used with knee replacements, infrequently with hip replacements in the United States, occasionally with hip revisions, in reverse shoulder operations, and in some spinal surgery. PMMA is also the material used in kyphoplasty (Kyphon KyphX HV-R Bone Cement), and PMMA suspended in bovine collagen (Artecoll) or a chemical colloid (MetaCrill) is used as an injectable dermal filler in cosmetics.29 Multiple components of bone cement have been reported separately to cause contact dermatitis and joint failure in exposed patients, as listed in Table II.

Methyl methacrylate (MMA) is primarily used in the manufacture of plastics, resins, and Plexiglas, which are subsequently used to make building panels, siding, molding, signs, skylights, and lighting fixtures. It is also used to impregnate concrete to render it water-repellent. Early nail porcelains (artificial nails) were composed of MMA, until the Food and Drug Administration recommended against its use in the early 1970s because of multiple reports of nail damage, contact dermatitis, and asthma in customers and nail technicians. Thirty-two states and 3 state

Abbreviations used
LPT-lymphocyte proliferation test
MMA- methacrylate
PMMA- polymethyl methacrylate
SI- stimulation index
TLR4- Toll-like receptor 4
WBC- white blood cell
cosmetology boards have prohibited its use, and the industry has replaced MMA with other molecules (eg, ethyl acrylate and 2-hydroxyethyl methacrylate) that may be as allergenic as MMA, and may cross-react with it. Other potential sensitizing exposures to methacrylates include their use in Krazy Glue (ethyl 2-cyanoacrylate) and Super Glue (ethyl-2-cyanoacrylate, PMMA, and hydroquinone) and in dentistry through their use in dental crowns and dentures.

The allergenicity of MMA is well documented with case reports of both contact dermatitis and asthma caused by exposure to bone cement in orthopedic surgeons, operating room nurses, and MMA in dentists and dental assistants.

**Who should be tested for metal sensitization?**

An excellent review and meta-analysis of the role of metal sensitivity testing in patients undergoing total joint arthroplasty was authored by Granchi et al in 2012.
studies was complicated by several different measures of sensitization, including both patch tests and in vitro lymphocyte proliferation tests (LPTs). Interestingly, the prevalence of sensitization was found to increase over time, from 16% in 1970 to 29% in June 2011, although part of the increase was attributed to the increasing numbers of tested allergens. The probability of having a metal allergy was almost 3 times higher in patients with a failed implant than in those with a stable implant (odds ratio, 2.8; 95% CI, 1.14-6.70; P = .02).

However, testing for sensitization by itself was not able to distinguish between stable and failed replacements because patients with implants overall have higher rates of sensitization to implant components than do patients without implants. The conclusion, therefore, is that there is no indication to test patients for implant sensitization if they have a well-functioning joint replacement. Such patients will have a higher likelihood of a positive reaction, which clinically is without meaning. The conundrum is how to determine when evidence for implant sensitization is clinically relevant in patients with joint failure.

Whether testing to implant components provides clinically meaningful results in patients with implant failure can be answered, in part, by outcome studies. A recent study reported on the patch test and outcome results of 41 postoperative patients referred for evaluation for chronic pain, joint loosening, and/or localized dermatitis at the site of the implant. Ten patients had clinically significant positive patch test results to a component of their implant, and 6 underwent joint revision to remove the allergic component(s). Symptoms resolved in all those who underwent joint revision but persisted unchanged in those who did not undergo revision, and the authors recommend that if patch testing suggests a potential allergic cause, then removal of the implant should be considered. Anecdotally, steroids and methotrexate have been used in a few patients sensitized to their implant, but no study has evaluated their efficacy. In another study of 80 patients with implant failure, 54% were found to be sensitized to a metal or bone cement relevant to their implant. The reported outcome scores of the 23 patients who underwent joint revision on the basis of the allergy evaluation were significantly higher (P < .0001) than those of similarly exposed allergic patients with a failed implant who did not undergo joint revision, or underwent joint revision without using the allergy results (unpublished data; Pacheco K et al 2015).

When does sensitization to implant components occur?

Preoperative patients with a history of reacting to metals have high rates of positive patch test results, indicating that sensitization occurred before the implant. There are few studies that have measured preimplant and postimplant contact allergy test data. One interesting study of 60 patients scheduled for arthroplasty found that 85% of those reporting a history of metal-induced dermatitis had a positive metal patch test result to nickel, palladium, cobalt, and/or chromium, and were implanted with hardware that did not contain the metal in question. This suggests that patients with a history of metal allergy should be tested before surgery to help select the implant. Two years after the implant, 48 (80%) of the original 60 took part in a follow-up evaluation. Interestingly, 5 patients (10%) with negative test results before surgery developed new metal patch test reactions (nickel, cobalt, and/or chromium) after the surgery that were associated with implant failure. Anecdotally, many patients with implant failure due to sensitization to implant components have no history of metal, methacrylate, or antibiotic reactivity (unpublished data; Pacheco K et al 2015).

How to establish the diagnosis of joint failure due to allergy to implant components?

As with all diagnostic dilemmas in medicine, the key to establishing the diagnosis of joint failure due to sensitization to implant components is to consider it in the first place. Because patients may be exposed to metals, methacrylates, and antibiotics in everyday life as well as in the orthopedic arena, Table III includes recommended screening questions to address whether the patient might have a history of allergy to orthopedic or dental components.

Patch testing remains the criterion standard for establishing a diagnosis of metal, bone cement, or antibiotic sensitization. Patch test extracts are available commercially from a number of companies (see Table IV), and some offer extract panels specific for surgical implant. It is important to determine the specific type of implant that is the concern because different metals and methacrylates are used in different implants. Using nonspecific panels can lead to irrelevant and/or persistent responses. For example, although patch testing to gold, platinum, and iridium is reasonable in a patient reacting to dental or cardiac implants, these are irrelevant to answer a question regarding a knee or hip implant. There are panels specific for dental implants as well as for dental personnel separately available. One exception to the use of implant-specific panels is the importance of adding dental-specific methacrylates to the joint implant panels because there is likely cross-reactivity, and exposure to a dental methacrylate may have been the source of a later reaction to bone cement (included in Table V).

The panel in Table V includes all the metals currently used in orthopedic implants that are known to be allergic, based on review of the material safety data sheets from major orthopedic supply companies. Bone cement extracts include the different allergenic components of the 2-part mix, along with the actual bone cement liquid and powder purchased from one of the orthopedic companies. Several studies indicate that commercial methacrylate extracts rapidly lose their potency after a few weeks, and hence become unable to detect relevant sensitization. This is the rationale for including actual bone cement, placing 3 to 4 drops of the liquid bone cement in one patch and a slurry of the bone cement powder with 3 to 4 drops of liquid bone cement in another, as a form of usage test. The list of antibiotics includes those used in orthopedic surgery and commercially available in extract form.

ORTHOPEDIC IMPLANTS CASE CONTINUED

You perform patch testing to the metals used in orthopedic implants, components of bone cement, and antibiotics that may be added to cement or sterile saline to lavage the surgical field. The patient asks you whether you are going to send blood tests for sensitization, but you are not sure of the validity of such tests.

In vitro assays to assess sensitization to metals

There remains debate between the orthopedic and allergist/immunologic literature over the best methods of demonstrating sensitization to implant components. Patch testing is generally regarded as the criterion standard to establish sensitization to metals and cements in the allergy/immunology sphere. It has the
TABLE III. Recommended screening questions to support the diagnosis of joint failure due to allergy to implant components

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you develop rash or itching to earrings, necklaces, watchbands, or jean snaps?</td>
<td>Have you ever worn artificial nails?</td>
</tr>
<tr>
<td>2. Have you ever worn artificial nails?</td>
<td>Have you ever used topical antibiotics such as bacitracin or Neosporin (contains bacitracin, neomycin, and polymixin B)?</td>
</tr>
<tr>
<td>3. Have you had local swelling, pain, or ulcers to dental implants, crowns, or dentures?</td>
<td>Have you ever used topical antibiotics such as bacitracin or Neosporin (contains bacitracin, neomycin, and polymixin B)?</td>
</tr>
<tr>
<td>4. Have you ever worked with Krazy Glue or Super Glue?</td>
<td>Have you ever used topical antibiotics such as bacitracin or Neosporin (contains bacitracin, neomycin, and polymixin B)?</td>
</tr>
<tr>
<td>5. Have you ever used topical antibiotics such as bacitracin or Neosporin (contains bacitracin, neomycin, and polymixin B)?</td>
<td>Did you develop a skin rash with their use?</td>
</tr>
</tbody>
</table>

The characteristics of some of these antigens help to boost both the specific and the innate immune response to them. Both nickel chloride and cobalt chloride have been shown to directly induce expression of intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin (an adhesion molecule involved in WBC chemotaxis, and expressed on endothelial cells after stimulation by cytokines). Nickel is a potent activator of dendritic cells by binding to histidines 456 and 458 of their surface Toll-like receptor 4 (TLR4), and activating the innate immune system inflammatory cascade; cobalt and palladium behave similarly through the TLR4 pathway. The TNF-α response to PMMA wear particles also involves signaling through MyD88/TLR4 pathways. Micrometer-sized titanium wear debris activates macrophages through an IL-4- and TLR4-independent pathway.

Filaggrin, a histidine-rich epidermal protein present in the stratum corneum, avidly chelates nickel and possibly other metal ions. It may thus prevent the passage of free nickel and other metal ions into deeper skin compartments in which these metals may interact with both the innate and specific immune systems. Persons with filaggrin null genotypes had a younger mean age at onset of nickel dermatitis (18.3 years vs 21.7 years; P = .09) and demonstrate increased skin reactivity at lower doses of nickel than did those with the wild-type genotype. The difference in skin test reactivity was not found in those with heterozygous variants.

In addition to immune activation, nickel has been shown to elicit immune tolerance. The site of a negative patch test result to nickel nonetheless shows infiltration of CD4+CLA+ cells and CD25+ T regulatory cells that suppress nickel-specific responses of peripheral blood CD25+ T cells. In contrast, CD25+ peripheral T cells from nickel-allergic individuals were unable to suppress nickel-specific CD4+ and CD8+ T-cell responses. IL-10 downregulates the production of stimulatory Th1 cytokines from PBMCs induced by incubation with nickel, although there is controversy as to whether IL-10 is produced by nickel-sensitized or nickel-tolerized subjects. An interesting study of titanium-induced cytokines and T-cell proliferation compared 14 healthy implant-free subjects with 6 symptom-free subjects with titanium dental implants. Those with symptom-free implants had lower cytokine responses (IL-1β, IL-6, and TNF-α) to titanium, but showed spontaneous production of IL-10, whereas none of the controls did so. This suggests that those with symptom-free implants may elaborate a tolerogenic baseline response.

**CASE CONTINUED**

The patient demonstrates strong patch test reactions to nickel and cobalt. You have decided not to conduct blood LPTs because you are not sure whether the results would be valid. What do you advise the surgeon?

Your first job is to identify the components and alloys of the patient’s implant(s) to determine whether his patch test reactions are relevant to the case. To do so, you will need the manufacturer and part numbers of the components that were implanted (Table VI). This information is usually found on the “sticker sheet” associated with the surgical record. Each component used (or opened and not used) has a peel-away sticker that lists the manufacturer and part and lot numbers and is kept on a specified record page attached to the operative
report. However, it is not routinely included in the operative report, and must be specifically requested. The patient record should include all implanted components, not just of the joint in question, because the history of reactivity should be consistent between similar implants. A reaction to cobalt in a patient with a failing left hip replacement of cobalt-chromium, and a well-performing right hip replacement of titanium alloy, is relevant. An equivocal reaction to the benzoyl peroxide component of PMMA bone cement in a patient with a problematic cemented knee replacement who has subsequently tolerated a PMMA kyphoplasty without problems is not clinically relevant. The information on implant contents is available either from the local company representative or can be obtained by directly calling the company. It is not always available from the company Web site. All commercially available bone cements contain similar components, although occasionally in slightly differing percentages, and so it is not necessary to contact the manufacturing company for the exact information. Whether the cement contains a dye (eg, barium sulfate and chlorophyll) or antibiotics will be noted on the sticker. Whether the surgeon has added extraneous antibiotics to the cement during the operation should be noted in the operative report.

**CASE CONTINUED**

The patient’s knee implant is made of a cobalt-chromium alloy that contains 60% cobalt, 33% chromium, 5% molybdenum, and 1% nickel. Like most knee replacements, it is cemented. Patch test results indicate that the patient is sensitized to both nickel and cobalt. Both together are not unexpected because about 30% of the patients sensitized to nickel are also sensitized to cobalt. You inform the surgeon that the patient is sensitized to cobalt and to nickel, and that in the absence of other common causes of joint failure, that is, infection and mechanical problems, the patient’s joint failure is most likely caused by his sensitization to implant components.

**What is the next step?**

There are 2 basic treatment options for the patient sensitized to his or her implant components, although both lack extensive data on which to base the treatment choice. The patient may be unwilling to undergo repeat surgeries to revise the implant, and may request immune suppression to decrease the inflammatory response. Although, anecdotally, patients sensitized to joint components have been treated with prednisone or methotrexate, there are no studies on the effectiveness of these treatments. One-year follow-up of 20 patients who were found to be sensitized to a component of their joint replacement but did not undergo joint revision showed that 75% of them were not at all better (unpublished data; Pacheco et al 2015), indicating a lack of

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### TABLE IV. Suppliers of patch test preparations

<table>
<thead>
<tr>
<th>Name/country</th>
<th>Address</th>
<th>Phone (toll-free):</th>
<th>Web site</th>
</tr>
</thead>
<tbody>
<tr>
<td>AllergEAZE</td>
<td>2150 29 Street NE, Unit 30</td>
<td>866-903-2671</td>
<td><a href="http://www.allergeaze.com">www.allergeaze.com</a></td>
</tr>
<tr>
<td>SmartPractice</td>
<td>Calgary, AB T1Y 7G4 Canada</td>
<td>866-903-2672</td>
<td></td>
</tr>
<tr>
<td>Almirall Hermall</td>
<td>Scholtzstraße 3 21465 Reinbek</td>
<td>49-40-727-04-0</td>
<td><a href="http://www.almirall.de">www.almirall.de</a></td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>49-40-722-92-96</td>
<td><a href="http://www.almirall.com">www.almirall.com</a></td>
</tr>
<tr>
<td>Brial allergen GmbH</td>
<td>Bövemannstr. 8 D-48268 Greven</td>
<td>49-2571-93-97-0</td>
<td><a href="http://www.brial.com">www.brial.com</a></td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>49-2571-93-97-20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>+46-0-40-46 67-00</td>
<td></td>
</tr>
<tr>
<td>Dormer Labs Inc/Chemotechnique</td>
<td>91 Kelfield Street #5 Toronto, ON M9W 5A3 Canada</td>
<td>866-976-7637</td>
<td><a href="http://www.dormer.com">www.dormer.com</a></td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>877-436-7637</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Customer service (toll-free): 1-800-878-3837</td>
<td>800-363-5040</td>
<td><a href="http://www.smartpractice.com">www.smartpractice.com</a></td>
</tr>
<tr>
<td>SmartPractice</td>
<td>3400 E. McDowell Rd. Phoenix, AZ 85008-7899 USA</td>
<td>1-800-926-4568</td>
<td><a href="http://www.smartpractice.com">www.smartpractice.com</a></td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>1-800-926-4568</td>
<td></td>
</tr>
<tr>
<td>Trolab/</td>
<td>Herrengraben 6 D-21465 Reinbek</td>
<td>+49-40-50-524-707-800</td>
<td><a href="http://www.smartpracticeeurope.com">www.smartpracticeeurope.com</a></td>
</tr>
<tr>
<td>SmartPracticeEurope</td>
<td>Germany</td>
<td>+49-40-50-524-707-801</td>
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</table>

### TABLE V. Recommended patch test panel for orthopedic implants

<table>
<thead>
<tr>
<th>Metal</th>
<th>Bone cement</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td>MMA</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Ethyl methacrylate</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Chromium</td>
<td>Benzoyl peroxide</td>
<td>Gentamycin</td>
</tr>
<tr>
<td>Manganese</td>
<td>N,N-dimethyl-para-toluidine</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Hydroquinone</td>
<td></td>
</tr>
<tr>
<td>Titanium</td>
<td>2-hydroxyethyl methacrylate</td>
<td></td>
</tr>
<tr>
<td>Aluminum</td>
<td>Bone cement liquid</td>
<td></td>
</tr>
<tr>
<td>Vanadium</td>
<td>Bone cement liquid &amp; powder</td>
<td></td>
</tr>
<tr>
<td>Tantalum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zirconium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niobium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Address</td>
<td>Phone/fax</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Aesculap (B. Braun Melsunger)</td>
<td>Aesculap Implant Systems, LLC 3773 Corporate Pkwy Center Valley, PA 18034</td>
<td>(Toll-free) Phone: 800-234-9179 Fax: 610-984-9096 Customer service (toll-free) Phone: 866-229-3002 Fax: 314-551-5991</td>
</tr>
<tr>
<td>Biomet</td>
<td>Biomet Orthopedics, LLC 56 East Bell Dr PO Box 587 Warsaw, IN 46581</td>
<td>Phone: 574-267-6639 Fax: 574-267-8137</td>
</tr>
<tr>
<td>Biomet Spine</td>
<td>310 Interlocken Pky Ste 120 Broomfield, CO 80021</td>
<td>Phone: 303-443-7500 Fax: 303-501-8444</td>
</tr>
<tr>
<td>Conformis</td>
<td>Corporate Headquarters: 28 Crosby Dr Bedford, MA 01730 Manufacturing Facility: 11 North Ave Burlington, MA 01803</td>
<td>Phone: 781-345-9001 Fax: 781-345-0147 E-mail: <a href="mailto:info@conformis.com">info@conformis.com</a></td>
</tr>
<tr>
<td>DePuy USA</td>
<td>A Johnson &amp; Johnson company Synthes, Inc, 1302 Wrights Lane East West Chester, PA 19380</td>
<td>Phone: 610-719-5000 Customer service (toll-free): Phone: 800-523-0322</td>
</tr>
<tr>
<td></td>
<td>Memphis Headquarters: 7133 Goodlett Farms Pkwy Cordova, TN 38016</td>
<td>Memphis (Orthopaedic Reconstruction, Trauma and Extremities) Customer service (toll-free) Phone: 800-238-7538 (local) Phone: 901-396-2121</td>
</tr>
<tr>
<td>Stryker</td>
<td>Stryker Global Headquarters: 2825 Airview Blvd Kalamazoo, MI 49002</td>
<td>Phone: 269-385-2600 Phone: 269-389-2300 Shared services Fax: 269-385-1062</td>
</tr>
<tr>
<td></td>
<td>Stryker Orthopaedics 325 Corporate Dr Mahwah, NJ 07430</td>
<td>Phone: 201-831-5000 Fax: 201-831-6288 Customer support (toll-free) Phone: 866-672-7747 OR assist hotline (toll-free) Phone: 877-946-9678</td>
</tr>
<tr>
<td>Wright</td>
<td>Wright Medical Technology, Inc, 1023 Cherry Rd Memphis, TN 38117</td>
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spontaneous improvement without any intervention. In contrast, of 23 patients similarly sensitized to a component of their joint replacement who underwent joint revision on the basis of allergy results and interviewed 1 year later, 74% were a lot or moderately better. Other smaller case series have also demonstrated improvement in patients sensitized to their implants who underwent joint revision to exclude the allergic component.6667

CASE CONTINUED
Final patient recommendations

The patient has undergone knee replacement with a cobalt-chromium-containing implant. Shortly after the procedure, he developed persistent pain and swelling that limits his activities. Other causes of joint failure, including infection and mechanical mismatch, have been ruled out. Patch test results demonstrate that the patient is sensitized to both cobalt and nickel; both are components of the alloy of his current knee prosthesis. You advise that the patient is unlikely to improve until the implant is revised to components to which the patient is not sensitized. His knee implant is revised to a titanium alloy, and 6 months after the revision, the patient is walking and pain free.

Over the past few years, whether allergy to metal and other implant components should be assessed as a cause of joint replacement failure has been actively discussed in the medical literature, along with the best approach of doing so (Figure 1). Although not without controversy, there is reasonable consensus that preoperative patients with a history of reacting to metal should be tested for sensitization before replacement to help choose the implant type.66 In 1 study described above,46 31 preimplantation patients were referred by their orthopedic surgeon for a self-reported history of metal reactivity. Of these, 21 (68%) showed a positive reaction to 1 or more metals and were implanted with hardware that did not have that metal as a component. All 21 patients did well without early joint loosening or local dermatitis. Nonetheless, there are case reports of patients with documented nickel and cobalt sensitization who have tolerated implants composed of these metals without problems.6869 A patient with evidence for sensitization to a joint component by patch test or LPT who nonetheless has a well-functioning joint is by definition tolerant to the implant. The larger issues of tolerance, how to measure it, and the conditions that may induce it have not, as yet, been resolved for orthopedic implants.

There is also debate as to the approach to patients with a failed implant in whom other common causes of joint failure, that is, infection and mechanical mismatch, have been ruled out. There is growing support that the next step in evaluating such patients is growing support that the next step in evaluating such patients is by defining tolerant to the implant. The larger issues of tolerance, how to measure it, and the conditions that may induce it have not, as yet, been resolved for orthopedic implants.

OTHER IMPLANTS

Although the issue of implant sensitization is less well studied in these fields, a number of other surgical devices and implants are made of materials that are capable of causing sensitization, with the potential of causing local or systemic inflammation and failure of the device.

Cardiac stents, patches, pacing devices, and valve replacements

Medicare utilization from 2001 through 2009 demonstrates that more than 1 million diagnostic catheterizations were performed yearly, with annual stent placement increasing from 275,037 in 2001 to a high of 399,558 in 2004, and then a gradual decrease to 322,034 in 2009.74 Global Industry Analysts, Inc, expects the global coronary stent market to reach $9.8 billion by 2017.75

Coronary artery stents are usually made from stainless steel 316L or a cobalt-chromium alloy F562 or L605 and may be coated with gold or Nitinol, a nickel-titanium alloy (Table VII). When bare metal stents were immersed in extraction media replicating human sweat, or a 0.1 mol/L cysteine solution, the metal was found to corrode, and nickel, chromium, cobalt, and gold were released. Lesser amounts of metals were released from coated stents. This indicates that metals can become available as haptens, which, when complexed with serum proteins, may cause immune-mediated reactions.7 Several companies, including Abbott Vascular and Medtronic, indicate on their Web sites that persons allergic to 316L stainless steel or L-605 cobalt-chromium alloy “may suffer an allergic reaction to this implant.” In-stent restenosis has been reported in patients sensitized to nickel and molybdenum76 and to gold.77 Although that finding has been challenged in a study of 149 patients from Denmark,80 there does appear to be an association between metal allergy and recurrent in-stent restenosis.81 Cases of failure or stenosis due to metal allergy have not been reported with drug-eluting stents,82 possibly because such drugs also suppress allergic inflammation around the stent.

Vascular patches and stents are frequently composed of Nitinol, with rare case reports of percutaneous patent foramen ovale device implantations in patients allergic to nickel that required surgical removal for persistent chest pain.8384 Other reactions to Nitinol-containing patent foramen ovale occluder devices include pericarditis and chronic atrial fibrillation. In 1 study, adverse events including chest discomfort, palpitations, and migraine headaches following patent foramen ovale and atrial septal defect closure with Nitinol-containing devices were significantly (P = .028) associated with nickel sensitization.46 Localized pain and dermatitis developed in a patient treated with a Nitinol superficial femoral artery stent, which resolved after stent removal.46

Pacemakers and implantable cardioverter defibrillators consist of a generator, often covered with a titanium capsule, and leads attached through the pacemaker’s header. Headers are composed of PMMA and silicone rubber (polydimethylsiloxane). The conductor wires are usually made of MP35N (Table VII), an alloy of nickel, cobalt, chromium, and molybdenum, and may have a silver core for high-voltage applications (mainly automatic implantable cardioverter defibrillators). The pacing electrodes are commonly made of a platinum (80%-90%)/iridium (10%-20%) alloy, and defibrillator leads are usually composed of platinum, platinum-iridium, or tantalum coated with platinum. Leads are typically insulated with polyurethane, silicone rubber, silicone-polyurethane copolymers, polytetrafluoroethylene (Teflon), or parylene. The metals and some of the urethane components are sensitizers. Most reported reactions consist of localized dermatitis, erythema, or itching, although local inflammation from sensitization to pacing components can also
cause device failure and systemic symptoms. Reactions have been reported to silicone present in the lead insulation, causing pain; titanium, causing edema and erythema; and polysulfone, polyurethane, and silicon rubber, causing a rash, pruritus, and tenderness. Symptoms resolved once the implant was replaced with nonallergenic components.

Repeated failure of a nickel-containing prosthetic mitral valve was reported in a patient allergic to nickel in 1978, with no further reactions when it was finally replaced with a nonnickel valve. Such a scenario was later avoided by placing a nonnickel valve initially in a similar patient. The newly available percutaneous mitral valve repair kit MitraClip treats mitral valve regurgitation by clipping together incompetent mitral valve leaflets using a device made of Grade 1 Elgiloy ASTM F1058 (cobalt, 39.0%-41.0%; chromium, 19.0%-21.0%; nickel, 14.0%-16.0%; molybdenum, 6.0%-8.0%; manganese, 1.5%-2.5%; and 0.10% maximum beryllium, with the balance being iron). There have been no reports to date of failure due to a nickel or other metal allergy to the device.

Nuss bar implants
Repair of a pes excavatum can be achieved by placing a stainless steel bar into the chest just posterior to the sternum and ribs and anterior to the heart and lungs. When the concave bar is rotated, the sternum expands out. Sensitization to any of the components of stainless steel, including nickel, chromium, and molybdenum, can cause localized edema, dermatitis, and lymphadenopathy, protuberant granulation tissue at the incision site, as well as pain, tenderness, or serous drainage with negative cultures for microorganisms. Rates of metal allergy causing localized reactions range from 2.2% to 6.4%, and testing for metal allergy has been recommended as part of the preoperative evaluation.

Gynecological intrauterine devices and implants
More women are choosing reversible contraception using intrauterine devices and subdermal implants versus pill and other hormonal methods, and these implants and intrauterine devices have the highest rates of satisfaction, use, and efficacy. However, many of these are made of metal, and numerous reports have documented adverse reactions to copper-containing intrauterine devices.

Dental implants
There is an extensive literature regarding sensitization to dental implants, which will not be reviewed here. Please see Kirshen and Pratt, Bakula et al, Pazzini et al, Schedle et al, Gawkrodger, Hamann et al, and Mallo Perez and Díaz Donado for excellent reviews of the subject.

CONCLUSIONS: SCOPE OF THE PROBLEM
On March 10, 1969, Dr Mark Coventry performed the first Food and Drug Administration-approved total hip replacement using a hip devised in 1962 by Sir John Charnley of England. The first total knee replacement in the United States was performed in 1968, and the condylar knee was developed by a group of researchers at Mass General Hospital in 1974. By 1976, 80,000 hip and 40,000 knee replacements a year were performed in the United States. Currently, more than 1 million joint replacements, primarily hips and knees, are performed yearly in the United States: estimates from the US National Hospital Discharge Survey in 2010 report 719,000 total knee replacements and 332,000 total hip replacements, or more than 1,051,000 combined joint replacements in 2010. Numbers are similarly high and rising in Canada, Europe, and Australia as well.

The primary recipients in the United States are of Medicare age, although the age range of patients receiving joint replacements is growing. A study of data between 2001 and 2007 that compared US and Ontario, Canada, joint replacement procedures found that there was a significant shift in hip and knee recipient ages to younger patients (P < .0001) for both. Those aged 20 to 49 years and 50 to 59 years showed the highest rates of growth, although the rates of all age groups, including those older than 80 years, increased. In addition to younger ages, the number of patients with comorbidities receiving implants is also increasing. A study of more than 3 million Medicare patients aged 65 years and older who received knee replacements between 2007 and 2010 included more patients with diabetes, obesity, heart failure, and chronic renal failure.

In 2004, aggregate hospital costs were $6.3 billion for knee replacements and $5.3 billion for hip replacements. Medicare is the largest payer for Joint replacements and paid more than $5 billion for primary and revision joint replacements in 2006. A large component of the cost is the price of the implanted...
Joint replacements have been calculated to cost more than the median annual income in 18 states. However, joint replacements are highly cost-effective from a societal standpoint. Patients with implants are able to remain active, continue working, and require fewer arthritis medications over time than do matched controls who did not undergo implant surgery. Numerous studies support the cost-effectiveness of joint replacements.

Of importance, from 10% to 20% of joint replacements per year are revision surgeries for joint failure—a diagnosis that includes any replaced joints that do not work properly. Just as the demand for joint replacements is expected to grow over the next 15 years, total hip and total knee revisions are projected to increase by 137% and 601%, respectively, between 2005 and 2030. Nonetheless, revision surgery is still a cost-effective option.

**FIGURE 1. Algorithm for approach to implant patients.** The figure details an approach to the assessment of sensitization to implant components in patients before implant surgery, and after failure of the implant once infection and mechanical issues have been excluded as causes: who should be evaluated, and how the results may be interpreted and applied. ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; CRPS, complex regional pain syndrome.
approach to improve function, relieve pain, and improve quality of life.\textsuperscript{125} Diagnosing sensitization to implant components before surgery, or after the first episode of failure, can be expected to significantly reduce the rates and costs of revision.

REFERENCES


101. Al-Sa