Clinical Reviews in Allergy & Immunology (2019) 56:72–85
https://doi.org/10.1007/s12016-018-8707-y

Allergy to Surgical Implants

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Published online: 15 September 2018

Abstract
Surgical implants are essential elements of repair procedures to correct worn out joints, damaged spinal components, heart and vascular disease, and chronic pain. However, many of the materials that provide stability, flexibility, and durability to the implants are also immunogenic. Fortunately, allergic responses to surgical implants are infrequent. When they do occur, however, the associated pain, swelling, inflammation, and decreased range of motion can significantly impair the implant function. Given the high numbers of joint replacements performed in the developed world, allergic reactions to orthopedic implants form the largest category of allergic responses. The most important allergens in this category include nickel, cobalt, chromium, and bone cement. These allergens are also the most important in reactions to spinal surgeries. Multiple cardiac and neurostimulatory devices are constructed of metals and adhesives that can be sensitizing in some individuals. Implantable pulse generators, important in cardiac pacemakers, gastric stimulators, and neurostimulators, may include components made of stainless steel, titanium alloy, platinum and iridium, epoxy resins, poly methyl methacrylates, and isocyanates, all of which are immunogenic in some patients. Cardiac stents and patches are often made of Nitinol, a composite of nickel and titanium. More surgical procedures are closed using skin glues, which are also capable of triggering a blistering contact dermatitis. Patch testing is the gold standard to determine sensitization, and this review provides a list of standard allergens to test for different implants. The patients most appropriate for testing include (1) pre-operative joint replacement patients with a prior history of skin reactions to metal jewelry, jean snaps, watch bands, metal glass frames, artificial nails, or skin glue; (2) post-operative joint replacement failure patients needing revision without an obvious cause such as infection or mechanical incompatibility; and (3) post-operative cardiac or neurological patients with localized rash, pain, swelling, or inflammation near or over the implant.

Keywords Surgical implant · Joint replacement · Joint failure · Rash · Metal allergy · Nickel · Adhesive allergy · Methyl methacrylate · Contact dermatitis

Introduction

Surgical implants rely on a number of materials selected on the basis of their strength, stability, pliability, durability, and other physical characteristics. Unfortunately, some of these materials also have allergenic properties that can cause immunological reactions and implant failure for a small number of patients. This review will provide background information on the number, kinds, and revision rates of orthopedic joint implants, as these are the great majority of surgical implants used in the USA. They form the largest category of Medicare expenditures and, accordingly, revision due to allergy creates both a physical and financial burden on patient, surgeon, and payer. Implant components, materials used, and reported cases will illustrate the range of orthopedic replacements and adverse outcomes reported. The materials and immune consequences of other implants, including cardiac components, pacemakers, and gastric and spinal stimulators, will be examined. While some surgeons express skepticism that allergy to orthopedic implants is a real condition, there is ample evidence in the published literature of both contact dermatitis and respiratory disease triggered by sensitization

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to the same materials used in surgical implants but in an occupational setting (reviewed in Table 2). Lists of implant materials, and suggested patch test extracts to use for each kind of implant, are provided in Tables 1, 3, 4, and 5. Finally, we will review some of the controversies and questions that are raised by the issue of sensitization to surgical implant components.

Orthopedic Implants—Background and Rates

Over 1 million joint replacements/year are estimated to be performed in the USA, likely an under-estimate, and joint replacement surgery is the single largest category of expense for Medicare. Knee and hip replacements are the most common types of surgery for those enrolled in the Medicare program, according to the Centers for Medicare & Medicaid Services. Estimates from Medicare data report 280,000 total hip replacements in 2009 at a cost of $12 billion [1], and 600,000 total knee replacements in 2010 at a cost of $9 billion/year [2]. These data do not include the numbers in non-Medicare recipients.

The 2010 prevalence of total hip and total knee replacement in the total US population was 0.83 and 1.52%, respectively. Prevalence was higher among women than among men and increased with age, reaching 5.26% for total hip replacement and 10.38% for total knee replacement at 80 years. These estimates corresponded to 2.5 million individuals (1.4 million women and 1.1 million men) with the presence of a total hip replacement and 4.7 million individuals (3.0 million women and 1.7 million men) with the presence of a total knee replacement in 2010. Secular trends indicate a substantial rise in prevalence over time and a shift to younger ages. Hence, in 2010, around 7 million Americans were living with a hip or knee replacement [3]. By 2015, the number of total knee replacements performed in the USA exceeded 1 million, a 2-fold increase in total knee replacement operations since 2005 [4].

Table 1 Metals and elements in alloys used in medical and surgical implants

Implant alloy	Alloy elements	Approximate percentage	Uses
Stainless steel SAE 316L	Iron	40–68 (Balance)	Cardiac/intravascular devices, orthopedic prostheses, plates, pins, nails, bolts, screws, fixators, surgical clips/staples
	Nickel	8.3–35	
	Chromium	20	
	Manganese	2	
	Molybdenum	2–3	
Cobalt-chromium-molybdenum steel	Cobalt	60 (Balance)	Cardiac/intravascular devices, orthopedic prostheses, plates, pins, nails, bolts, screws, fixators, surgical clips/staples, dental implants, and restorations
	Chromium	27–30	
	Molybdenum	5–7	
	Nickel	< 0.5	
	Iron	< 0.75	
	Manganese	< 1	
	Tungsten	< 0.2	
	Aluminum	< 0.1	
	Titanium	< 0.1	
Vitallium™	Cobalt	61	Orthopedic prostheses, plates, pins, nails, bolts, screws, fixators
	Chromium	32	
	Silicon	0.5	
	Manganese	0.5	
	Molybdenum	5.6	
	Iron	None	
Titanium alloy	Titanium	90	Orthopedic prostheses, plates, pins, nails, bolts, screws, fixators, pacemaker shells, surgical clips/staples
	Aluminum	5.5–6.5	
	Vanadium	3.5–4.5	
	Nickel	0.012–0.034	
Titanium-tantalum-niobium	Titanium	53	Orthopedic devices
	Niobium	25	
	Tantalum	7	
	Zirconium	5	
Nitinol	Titanium	55	Cardiac/intravascular devices, patent foramen ovale and septal defect devices and implants, bone anchors and staples, Essure contraceptive device, urological devices, orthodontics
	Nickel	45	
Oxinium™	Zirconium (oxidized)	97.5	Orthopedic joint prostheses
	Niobium	2.5	

Schalock PC, Menne T, Johansen JD, et al. Hypersensitivity reactions to metallic implants—diagnostic algorithm and suggested patch test series for clinical use. *Contact dermatitis*. 2012;66:4–19

Table 2 Other reports of allergic disorders associated with commonly used surgical materials

Material	Reference	Findings
General		
	Keskinen H, Kalliomäki PL, Alanko K. Occupational asthma due to stainless steel welding fumes. Clin Allergy. 1980 Mar;10(2):151–9.	2 welders with OA caused by stainless steel welding. One with contact dermatitis to chromium. Positive SIC in both to welding fumes. Welding fumes contain significant amounts of chromium and nickel, which may be the etiological agents.
	Nemery B. Metal toxicity and the respiratory tract. Eur Respir J. 1990 Feb;3(2):202–19.	Bronchial asthma caused by platinum, nickel, chromium, and cobalt on the basis of allergic sensitization.
	Arrandale VH, Liss GM, Tarlo SM, Pratt MD, Sasseville D, Kudla I, Holness DL. Occupational contact allergens: are they also associated with occupational asthma? Am J Ind Med. 2012 Apr;55(4):353–60.	Review of occupational materials causing both contact dermatitis and asthma. The 7 most common occupational causes were epoxy resin, nickel, cobalt, chromium, p-phenylene diamine, formaldehyde, and glutaraldehyde.
Nickel		
	Malo JL, Cartier A, Doepner M, Nieboer E, Evans S, Dolovich J. Occupational asthma caused by nickel sulfate. J Allergy Clin Immunol. 1982 Jan;69(1 Pt 1):55–9.	A 28 years old developed asthma in a metal plating factory. PST+ to $NiSO_4$ at 10 mg/mL, positive early asthmatic response to SIC, + IgE antibody to $NiSO_4$-HSA antigen.
	Estlander T, Kanerva L, Tupasela O, Keskinen H, Jolanki R. Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. Clin Exp Allergy. 1993 Apr;23(4):306–10.	2-year work grinding nickel castings. Developed contact urticaria, rhinitis, and asthma at work. PST, IgE RAST + nickel, PT + nickel, and SIC to $NiSO_4$ showed late asthma reaction.
	Sandhu A, Jacob SE, Vassantachart J. Dermatologic surgical implications of nickel allergy. Dermatol Surg. 2015 Nov;41(11):1335–7.	- Disposable electrocautery tip caused pruritic erythematous patch around wound × 2 days - Hypodermic needles caused itchy eruption at site of blood draw - Stainless steel surgical staples caused local dermatitis - Surgical metal clamps caused eczematous rashes, blisters, drainage, edema, and pruritus.
Cobalt		
	Sauni R, Linna A, Oksa P, Nordman H, Tuppurainen M, Uitti J. Cobalt asthma—a case series from a cobalt plant. Occup Med (Lond). 2010 Jun;60(4):301–6.	22 cases of cobalt asthma from a cobalt plant in Finland, confirmed by SIC with cobalt. Incidence was higher in jobs with higher cobalt exposure levels.
	Walters GI, Robertson AS, Moore VC, Burge PS. Cobalt asthma in metalworkers from an automotive engine valve manufacturer. Occ Med 2014;64:358–64.	14 metalworkers diagnosed with cobalt asthma with sensitization to cobalt chloride demonstrated in 7/7 by SIC.
Chromium		
	Bright P, Burge PS, O'Hickey SP, Gannon PF, Robertson AS, Boran A. Occupational asthma due to chrome and nickel electro-plating. Thorax. 1997 Jan;52(1):28–32.	Chromium induced asthma in 7 workers in metal electroplating works confirmed by positive SIC to potassium dichromate [$K_2Cr_2O_7$] and 2 also to nickel SIC.
	De Raeve H, Vandecasteele C, Demedts, Nemery B. Dermal and respiratory sensitization to chromium in a cement floorer. Am J Ind Med 1998;34:169–176.	Worker laying concrete floors × 34 years developed eczema on hands and lower arms, and SOB, confirmed by positive patch test and SIC to [$K_2Cr_2O_7$]
	Leroyer C, Dewitte JD, Bassanets A, Boutoux M, Daniel C, Clavier J. Occupational asthma due to chromium. Respiration. 1998;65(5):403–5.	A 28-year-old roofer with cough, shortness of breath, wheezing, rhinitis, and headaches triggered by sawing corrugated fiber cement, positive SIC to [$K_2Cr_2O_7$].
	Lockman LE. Case report: allergic contact dermatitis and new-onset asthma. Chromium exposure during leather tanning. Can Fam Physician. 2002 Dec;48:1907–9.	Leather worker in furniture factory, developed contact dermatitis on exposed skin, chest tightness and SOB. Positive patch test to chromium.
Polymethyl methacrylate (PMMA)		
	Fries IB, Fisher AA, Salvati EA. Contact dermatitis in surgeons from methylmethacrylate bone cement. J Bone Joint Surg 1975;57-A(4):547–9	13 cases of dermatitis in surgical personnel handling bone cement, including 9 in orthopedic surgeons. 7/9 were patch test + to PMMA.
	Scolnick B, Collins J. Systemic reaction to methylmethacrylate in an OR nurse. J Occ Med 1986;28(3):196–8	OR nurse developed HA, SOB, chest heaviness, and blotchy erythroderma of exposed skin when bone cement mixed in the OR.
	Villar RN, Johnston FG, Scott PM. Occupational asthma due to methyl methacrylate bone cement. Brit Med J 1986;292:1597.	Commentary on reports of contact dermatitis and asthma to PMMA in surgical personnel.
	Savonius B, Keskinen H, Tuppurainen M, Kanerva L. Occupational respiratory disease caused by acrylates. Clin Exp All 1993;23:416–24.	18 cases of respiratory disease, including 15 asthma and 3 rhinosinusitis caused by cyanoacrylates and methyl methacrylates, confirmed by patch testing.
	Kirby BS, Doyle A, Gilula LA. Acute bronchospasm due to exposure to PMMA vapors during percutaneous vertebroplasty. Am J Roent 2003;180(2): 543–4.	Radiology technician developed SOB, watery eyes, and rhinorrhea after exposure to PMMA vapors during a vertebroplasty procedure.

OA occupational asthma, *SIC* specific inhalational challenge, *PST* prick skin tests, *HSA* human serum albumin, *SOB* shortness of breath, *HA* headache, *PT* patch test

Since many people receiving knee replacements are elderly, Medicare picks up most of the cost of such procedures. In response to this huge rise in expenditures, Medicare is experimenting with ways to reduce the cost of procedures by the use of bundled payments for lower extremity joint replacement episodes.

It is important to note that joint replacement is highly effective surgery, resulting decreased morbidity and measurable improvements in mobility for the majority of patients. It has been considered a highly effective surgical intervention for osteoarthritis that predominantly affects older patients. Most studies have found favorable cost-effectiveness analyses for these interventions, indicating that the procedure significantly improves quality of life and reduces pain, disability, and direct costs for arthritis care [5] and also shows that it lengthens the time of employment for some patients [6–8].

However, because the USA does not keep a national registry of joint replacements, the number of procedures performed per year in this country is difficult to assess precisely. Recently, the AAOS (American Academy of Orthopaedic Surgeons) has announced plans to integrate the American Joint Replacement Registry (AJRR) with the AAOS in order to create a national database that captures a range of orthopedic conditions and procedures. The AJRR will specifically provide hip and knee procedure registries for the AAOS [9].

Failure and Revision Rates

Similarly, there are limited data available for the percentage of joint replacements that fail. Statistics from the AAOS website (www.AAOS.org) suggest that the rates of joint failure have remained stable at about 10% of all joint replacements. An older US study reviewing Medicare data alone reported that 250,000 primary TKAs (total knee arthroplasty) were performed in 2009 and 200,000 revision TKAs in the same year, although the revision numbers also refer to procedures done over the previous 20 years [10]. Annual reimbursements for revision hip procedures constituted 20% of all hip procedures, compared to knee revision costs constituting 9% of all knee surgery costs. After reviewing the results from joint registries in Sweden, Norway, Finland, Denmark, Australia, and New Zealand, these authors concluded that total hip and knee replacements show revision rates of 6% after 5 years and 12% after 10 years [11]. Revision rates for total ankle replacement, based on similar registries, were higher and estimated at about 10% at 5 years, of which 40% of cases were for aseptic loosening [12].

Importantly, most revision surgery is more complicated, and more expensive, than primary joint replacements, and those costs are not fully compensated. Medicare reimbursements constitute approximately 60% of each submitted procedure charge and do not cover the entire costs associated with joint replacement revisions [10]. Currently, Medicare is moving to a bundled payment initiative for lower extremity joint replacements, a system in which the hospital receives a set amount per procedure to cover payment for all care related to hip or knee replacement from the surgery until 90 days after [13]. Hence, complications and adverse outcomes from joint replacement up to 3 months post procedure, in addition to affecting the patient, will not receive extra coverage for the hospital or provider.

Causes of Implant Failure

There are several commonly accepted conditions that are considered to be the most frequent causes of joint replacement failure. These include infection and mechanical issues of size, placement, orientation, or kind of implant. One review of the causes of TKA failure distinguished between early failure, defined as < 2 years after the implant surgery, and late failure, including those that failed two or more years post implant. Aseptic loosening was the most common cause of failure overall, accounting for 40% of all revision procedures. Infection was the most common cause of early knee revision at 38%, followed by loosening (23%), instability (6%), and arthrofibrosis (4%)—excessive scarring post-surgery. Aseptic loosening of the implant was the most common cause of late revisions at 51.4%, followed by infection (22%), instability (10%), and arthrofibrosis (4%). The remaining causes were primarily related to mechanical issues in both groups [14]. Similarly, the most common indications for hip replacement revision surgery were predominantly aseptic loosening in 51% of 1366 hip revisions, followed by instability in 15%, wear in 14%, and infection in 8% [15]. A study of 2107 first-time revision THAs (total hip arthroplasty) from 30 tertiary centers in France was collected from January 1, 2010 to December 31, 2011. The primary causes for revision were mechanical loosening (42%), periprosthetic fracture (12%), infection (11%), wear/osteolysis (11%), dislocation (10%), surgical technique error (6%), and implant fracture (3%) [16]. An earlier review of 225 patients who underwent 237 hip revisions in the USA found that the most common cause of failure was aseptic loosening in 52%, instability in 17%, and infection in 5.5%. Half of the revisions were performed < 5 years after the index arthroplasty, with 33% due to instability and 24% resulting from infection.

Well-documented risk factors for poor outcomes for joint replacement include diabetes, cigarette smoking, osteoporosis, hemarthrosis, and aseptic loosening. Interestingly, and especially in the orthopedic literature, allergy, i.e., sensitization to implant components, is rarely, if ever, considered. For example, the website www.orthoinfo.aaos.org lists infection, blood clots, implant wear, limited range of motion, continued pain, and neurovascular injury as possible

complications of joint replacement surgery, but allergy to implant components is not included.

Yet many of the components of joint replacements include highly sensitizing materials, well documented in other areas of medicine to cause sensitization. Table 1 is a list of the most commonly used alloys and implant components in orthopedic joint replacement and spinal surgery.

The allergy, dermatology, and occupational medicine literature well documents the typical manifestations of sensitization to the metals and cements used in orthopedic surgery. Table 2 is a partial summary of the reported disorders associated with the most commonly used materials in settings other than the surgical patient. This robust literature clearly demonstrates that these materials are capable of causing sensitization and disease in exposed individuals. In these examples, the exposure is either dermal or inhaled via particles or vapors.

The extrapolation of these examples to orthopedic materials remains poorly documented to date. Yet it is likely that materials capable of sensitizing through dermal and inhaled routes should be equally capable of eliciting sensitization and disease through internal routes as well, although the specific pathways and cells involved may differ.

Review of Reports of Implant Allergy

There is inherent difficulty in conducting prospective studies of the effect of a pre-existing history of metal or methacrylate sensitization on joint replacement outcomes. Hence, the reports that exist are incidental and anecdotal.

The earliest reports of metal sensitivity in patients with total joint replacements date from soon after the initial major joint replacements. The first metal hip replacement was performed by American surgeon Dr. Austin Moore in 1940, and the first total knee replacement in 1968, although it was in 1974 that the modern condylar knee joint was first implanted. E.M. Evans and colleagues presented the argument in 1974 that cobalt chrome surfaces release metal ions into the local tissue, which pass into the blood stream and are presented to all body tissues. In certain patients, such metal release results in tissue sensitization which can be detected clinically by patch testing. Release of metal was postulated to cause obliteration of local blood vessels supplying the bone, leading to necrosis and loosening, although other immune mechanisms may in fact be responsible. This study examined 14 patients with loose cobalt/chromium hips ($n = 12$), elbow ($n = 1$), or knee replacements ($n = 1$) with patch testing to cobalt, chromium, and nickel. Of these, nine were sensitized to one or more metal components, including seven to cobalt, one to cobalt and nickel, and one to chromium [17]. In contrast, 24 patients with secure hip replacements were not sensitized to any implant components. A study published the next year examined 50 patients with hip and knee replacements, of whom 26 had failed [18]. Of the 26 patients with failed implants, three failed due to fracture of the appliance, and four were infected. Of the remaining 19, 74% ($n = 14$) were sensitized to cobalt, chromium, nickel, and/or vanadium by patch testing. Of the 24 patients with a stable prosthesis, only 4 were sensitized to cobalt and/or nickel (17%).

However, rates of positive patch test reactions to metals are generally higher in patients with implants than those without, although they tend to be higher still in those with poor outcomes. But not all patients with a documented history of metal allergy will develop implant failure to a joint replacement containing the allergenic metal. For example, a case was reported of a woman with pre-operative positive patch testing to nickel, cobalt, and chromium, who nonetheless tolerated a cobalt/chromium knee prosthesis without failure after 2 years [19].

Thirty years later, D. Granchi and colleagues examined by patch testing to implant components a total of 66 candidates for total hip replacement (THR = THA), 53 with stable THRs, and 104 with THR loosening. Patch testing was not able to discriminate between stable and failed implants. However, sensitivity to at least one allergen, especially bone cement, as well as a positive history of metal reactivity, was associated with decreased THR survival [20]. A subsequent study of 94 knee implant patients (20 pre-implant, 27 well-functioning, and 47 loosened implants) found a higher frequency of positive skin reactions to metals after knee replacement, either stable or loose (20% in pre-op patients, 48% in stable TKAs, and 60% in loosened TKAs, $p = 0.001$). TKA failure was four times more likely in patient with symptoms of metal sensitivity before the procedure.

In contrast, 60 pre-implantation patients were patch tested to chromium, cobalt, nickel, copper, palladium, aluminum, vanadium, titanium, and molybdenum, and 48 of the original cohort post-implant were again tested [21]. About 22% of the pre-op patients were patch test positive to one or more metals, including 85% of those with a history of metal dermatitis. Patch test positive patients received implants not containing the allergenic metal, and none had symptoms post-operatively. Contact allergy to metals was found in 25% of the post-op patients, including five (10%) with new metal reactions. All five reported symptoms to the implant which contained the new metal(s). A different study compared 66 hip or knee implant patients with complications to 26 without complications and found that 22/66 (33%) of those with complications were sensitized to nickel, cobalt, and/or chromium and 32% to bone cement components, compared to the asymptomatic controls, where 4% were metal sensitized and 15% allergic to gentamicin [22].

An excellent study of 31 pre-implantation patients referred for metal testing based on a clinical history of metal reactivity (90%) found that 68% (21/31) were sensitized to one or more metals. All were implanted with a different metal selected on the basis of patch testing, and all did well without skin eruptions or early loosening. In the same study, 15/41 (37%) post-

implantation patients with chronic pain at the implant site were patch test positive to one or more metals, of which 10 reactions were relevant to the implant. Over half gave a clinical history of metal reactivity before the surgery. Of the 10 patients with relevant metal sensitization, 6 chose to revise the implant to one to which they were not allergic and all experienced relief of their joint related symptoms. The four who did not undergo implant revision had no change in theirs [23].

The prevalence of metal allergy in patients with metal on metal hip arthroplasties has been investigated because of higher failure rates. The histology of a revised group of 16 patients with failed metal on metal (MOM) hip replacements showed that lymphocyte and plasma cell dominated inflammation associated with severe fibrin deposition and macrophages, suggestive of a hypersensitivity reaction. In 13/16 (81%), sensitization to metals was established to cobalt, chromium, nickel, molybdenum, and/or manganese [24].

The components of bone cement include several sensitizers associated with joint replacement failure. For example, failure of knee and shoulder replacements due to sensitization to benzoyl peroxide, a component of bone cement, and confirmed by patch testing, has also been documented in several reports [25–27]. Sensitization to *n*,*n*-dimethyl-*para*-toluidine (DMT) was determined as the cause in 7/15 patients with early aseptic loosening of cemented hip replacements, compared to 0/25 with a stable THR, 0/25 pre-operative patients, and 0/5 with an infected THR [28]. A dermal reaction initially attributed to infection was subsequently identified as hypersensitivity to polymethylmethacrylate following a shoulder hemiarthroplasty requiring the use of bone cement [29].

In summary, the majority of patients with a pre-operative history of metal reactivity were found to be patch test positive to one or more metals. Such patients implanted with a metal prosthesis to which they were not sensitized had good outcomes. Patients post-implant generally have higher rates of patch test positivity to metals, including those with well performing implants. However, post-implant patients with complications who are found to be sensitized to an implant component do very well when revised to a non-allergic implant, whereas those not revised do not improve. Taken together, these reports indicate that sensitization to implant components is a cause of joint failure, and revision to a non-allergic component improves these outcomes. Table 3 lists the testing components recommended for both pre-operative and post-operative joint replacement patients.

Histopathology of Some Failed Implants Is Consistent with an Immune Mechanism

There are only so many ways a failed joint replacement can present. Common symptoms include pain, swelling, warmth, decreased range of motion, loosening or instability, and itching or burning on occasion. Unfortunately, such symptoms do not designate a cause. Although dermatitis over the surgical site is a well-recognized indication of sensitization to the internal implant, this is a relatively rare occurrence. Among common symptoms of failure, a number are caused by allergy and a localized inflammatory response to implant components. So, for example, aseptic loosening and instability can be triggered by a local inflammatory response caused by sensitization to metal or bone cement components, as well as by infection, cement failure, or poor bone formation. In such cases, cultures of synovial fluid and intra-operative frozen sections are negative for infection [30].

The term ALVAL ("aseptic lymphocyte-dominated vasculitis-associated lesion") was suggested by H-G Willert and colleagues as consistent with a delayed type metal hypersensitivity reaction. They studied the histology of 19 patients with failed MOM total hip replacements and found characteristic features of a diffuse, perivascular infiltrate of T cells, B cells, and plasma cells associated with macrophages, a massive fibrin exudate, and areas of necrosis [31]. In other cases of implant sensitization, histopathology at the time of revision demonstrated lymphocyte dominated peri-implant inflammation consistent with an immune response, seen in 20/25 failed TKAs [32] and 13/16 failed THAs [24]. One study of 52 revised MOM resurfacing hip arthroplasties found an inflammatory cell infiltrate of macrophages and lymphocytes in the pseudo capsules of 86%, containing CD68+/CD14+/HLA-DR+ macrophages. Discrete granulomas with macrophages and giant cells were seen in the 13 cases with pseudotumors and 3 cases of loosening. Lymphoid aggregates containing CD3+ T cells and CD20+ B cells were common, associated with scattered plasma cells. Results were suggestive of both cytotoxicity and hypersensitivity to metal particles [33].

Allergic Reactions to Other Surgical Implants: Cardiac Associated Devices

Multiple cardiac and neurostimulatory devices are constructed of metal, epoxies, and methacrylates, which can be sensitizing in some individuals. Here again, the presentation may be one of localized or systemic inflammation, as well as localized rash or itching suggestive of typical allergic reactions. Cardiac devices include coronary and other arterial stents, percutaneous patent foramen ovale occluders, valves, pacemakers, and ICDs (Implantable Cardioverter Defibrillators). Early coronary stents were made of bare metal, usually stainless steel that had the problem of in stent restenosis occurring in 16–33% of the stents deployed. Some cases of in-stent restenosis were associated with nickel and molybdenum contact allergies [34, 35]. Most coronary stents currently used are drug eluting. These typically employ sirolimus, paclitaxel, or

Table 3 Suggested patch test panels for orthopedic implants

Metals	These include the sensitizing metals utilized in stainless steel, cobalt/chromium, titanium, and Oxinium™ alloy implants.
	• Nickel
	• Cobalt chloride, cobalt sulfate
	• Potassium dichromate
	• Molybdenum
	• Manganese
	• Titanium, titanium oxalate
	• Aluminum
	• Vanadium
	• Zirconium
	• Niobium
	• Tantalum
Bone cement	These include the major components of bone cement and those that strongly cross-react with polymethyl methacrylate.
	• Polymethyl methacrylate (PMMA)
	• 2-HEMA (2-hydroxyethyl methacrylate)
	• Benzoyl peroxide
	• *n*,*n*-dimethyl-*para*-toluidine (DMPT)
	• Hydroquinone
	• Liquid bone cement
	• Liquid plus powder bone cement
Antibiotics	These may be added to bone cement or to sterile saline for surgical irrigation.
	• Bacitracin
	• Neomycin
	• Gentamycin
Skin glues	Incisions may be closed using skin glue composed of cyanoacrylates.
	• Dermabond® and SurgiSeal®: 2-octyl-cyanoacrylate.
	• Histoacryl®, Indermil®, GluStitch®, GluSeal®, PeriAcryl®, and LiquiBand®: *n*-2-butyl-cyanoacrylate
	• Epiglu®: ethyl-2-cyanoacrylate

variants of these drugs that are usually completely eliminated after 30 to 90 days of implantation.

Paclitaxel was originally isolated from the bark of the Pacific yew tree, *Taxus brevifolia*, in 1971, and suppresses cell proliferation as well as having anti-angiogenic effects. Hypersensitivity to Paclitaxel is not uncommon, and infusions of the drug are usually given concomitant with steroids and diphenhydramine to reduce the risk of reactions [36]. Hypersensitivity to a paclitaxel eluting stent, presenting with disseminated itching and hives, asthma, and acute synovitis, has been reported. The patient was treated initially with IV and then oral antihistamines for a month, until all stent-bound paclitaxel was assumed to be eluted, and the allergic reactions subsided [37]. Sensitization to other components of drug eluting stents, including the metal, is felt to be a cause of late in-stent stenosis [38], although the incidence of allergic reactions to stent components is difficult to quantitate. Composite metals, including nickel, cobalt, chromium, and gold, are released from coronary stents [39]. Stents retrieved after implantation show fretting, pitting, calcium deposits, and corrosion leading to metal release and deposits in surrounding tissues [40]. These reports suggest that metals locally released from the implant are capable of causing local allergic tissue reactions in susceptible individuals. A correlation between contact allergy to gold, use of a gold-plated stent, and chest pain has been reported [41]. However, an assessment of 147 patch test positive patients who had undergone placement of a metal coronary artery stent showed no association of in-stent restenosis with nickel or chromium allergy that had previously caused dermatitis [42]. Thus, the association between metal allergy and stent restenosis remains unclear and is probably of lesser importance as a cause of stent failure, given the volume of procedures done yearly compared to the very low rates of reported allergic reactions.

The association between nickel allergy and peripheral stent failure or dermal reactions is clearer. There are case reports of a generalized dermatitis in a nickel and cobalt allergic woman with an abdominal aortic aneurysm repaired with a Nitinol

(nickel and titanium alloy) endograft [43] and a similar severe generalized dermatitis in a nickel allergic patient with a Nitinol stent placed in the popliteal artery [44]. A Nitinol stent placed in the right femoral artery of two different patients with nickel allergies caused generalized severe pruritus and an eczematous dermatitis worse on the right leg. Symptoms completely resolved after the stent was replaced with a saphenous vein graft in one hand [45] and a PTFE interposition graft on the other [46]. Occlusion of a Nitinol biliary stent was reported in a different nickel allergic patient [47].

There are several case reports of adverse reactions to use of the Amplatzer atrial septal defect occluder composed of Nitinol. In one, the patient developed chest pain, dyspnea, and migraine headaches immediately after closure of a patent foramen ovale with the Amplatzer device. After being found patch test positive to nickel, the umbrella device was removed and the foramen was closed with polypropylene sutures, with resolution of all symptoms [48]. In another, a secundum atrial septal defect (ASD) with left to right shunt was repaired with an Amplatzer occluder device. Immediately after the surgery, the patient developed transient, mild right hand weakness, and paresthesias with decreased reflexes and later onset of migraine headaches and retrosternal chest pain. All symptoms were resolved after removal of the device and repair of the ASD with an autologous pericardial patch [49]. A larger study evaluated nine patients who were patch test positive to nickel and underwent interatrial shunt device closure, of whom eight developed a post-procedure "device syndrome" characterized by chest discomfort, exertional dyspnea, and asthenia that began within 24 h of the procedure. Six received the high nickel Nitinol Amplatzer device and two the low nickel Premere device. In one, the syndrome resolved spontaneously after 5 weeks; the other seven were treated with 10 mg/day of prednisone and 75 mg/day of Clopidogrel plus the usual dose of 100 mg/day of aspirin. All symptoms resolved after 1 week of treatment [50]. The authors attribute the device syndrome to the documented nickel allergy, as none of the 37 patients without nickel allergy who completed the procedure developed device syndrome symptoms.

Cardiac and neurostimulators are typically composed of a number of different metal alloys, along with plastics, resins, and glues, all of which are capable of causing sensitization. There are numerous case reports of contact dermatitis and/or systemic reactions to different components of cardiac pacemakers. The presentation can include localized tenderness and pain over the implantation site, a localized rash, itching and tenderness with edema and erythema [51], painful eczema [52] or even systemic hypotension, malaise, nausea and vomiting, and fever and chills associated with obstruction to vascular flow at the lead entry site in the subclavian vein [53]. Patch testing in the different cases showed positive reactions to titanium (pacemaker capsule [54];), nickel and cobalt (present in leads), toluene di-isocyanate (TDI, a polyurethane used in lead insulation [54];), and methylenedianiline (MDA, present in medical grade epoxy). In each case, symptoms resolved when the pacemaker was removed, with no evidence of infection as the cause.

Allergic Reactions to Other Surgical Implants: Neurologic Devices

There are case reports of reactions to neurostimulators, presenting as localized burning and itchy erythema [55], or as a delayed generalized erythematous papular rash with serous exudate from the receiver site [56]. In the latter case, the reactions were attributed to silicone shavings based on patch testing, although the exact nature of the allergen was not identified.

Adverse neurologic outcomes have been observed in nickel allergic patients with nickel containing neurologic implants [57]. A chronic headache and localized erythema over a parietal-occipital cranioplasty was identified as the presentation of a polymethyl methacrylate allergy to the Palacos cement used to close a skull defect. The allergy was confirmed by patch testing to poly methyl methacrylate, and symptoms resolved once the PMMA patch were removed. The defect was later closed with a bioceramic implant without incident [58].

Allergic Reactions to Other Surgical Implants: Abdominal Devices

Surgical clips made of tantalum caused persistent right upper quadrant abdominal pain and urticaria beginning 2 years after a cholecystectomy. All clips were removed, of which two were visibly corroded, and biopsy of the local tissue showed a giant cell reaction. Symptoms resolved completely 2 months after removal [59]. In summary, predominantly localized symptoms of pain and swelling, sometimes associated with an itchy localized rash, are the typical presentations of sensitization to stents and other implants. Generally, symptoms resolve once the implant is removed or replaced with non-allergenic materials. Table 4 lists the components and recommended patch test materials for cardiovascular and other surgical implants.

Comment on Titanium Sensitization

Although titanium and titanium alloys (90% Ti/6% Al/4% V) are frequently used in dental implants, spinal fixation, and joint replacement hardware, well-documented titanium allergy is rare. The currently available titanium patch test extracts are not felt to be reliable because of low

Table 4 Suggested patch test panels for implantable stimulators, stents, and surgical clips

Comment:	Implantable pulse generators contain similar components, although not always the same, and information from the manufacturer's website may be too vague to be helpful. In addition to metals, urethanes, and epoxies, these may also use silicones, poly ether ether ketone (PEEK), polyethylene terephthalates, polysulfone, and parylene, which are not reported to cause allergic reactions and to which there are no commercially available extracts.
Example:	
Case	• Titanium alloy (Ti/Al/V)
Connector block	• Stainless steel: nickel, chromium, manganese
Port Plug: MP35N alloy	• Nickel, cobalt, chromium, molybdenum
Contacts, leads	• Platinum, iridium
Port plugs	• Polyurethanes: TDI, MDI
Headers	• Epoxy resins: bisphenol A epoxy resin, epichlorohydrin, *o*-cresyl glycidyl ether, bisphenol F, and ethylenediamine dihydrochloride
Lead body	• Polyurethanes: TDI, MDI
Suture sleeves	• Silicone (inert)
Recommended extract panel:	
• Nickel	• TDI (toluene diisocyanate)
• Chromium	• MDI (methylene diphenyl diisocyanate)
• Cobalt	• Bisphenol A epoxy resin
• Manganese	• Epichlorohydrin
• Molybdenum	• *o*-Cresyl glycidyl ether
• Platinum	• Bisphenol F
• Iridium	• Ethylenediamine dihydrochloride

epidermal penetration of the commercially available titanium salts. Case reports of titanium reactivity causing implant failure either poorly document the titanium allergy or, on further examination, are attributed to other materials. A recent excellent review nicely summarizes the studies [60].

Approach to the Patient with Possible Implant Allergy

Who Should Be Tested?

There are two groups of patients who should be tested for metal, bone cement, and antibiotic allergies as relate to orthopedic implant allergy. Those awaiting implants with a credible history of skin reactivity to metal, including jewelry, watch bands, jean snaps, bra snaps, tools, and the like, should be tested before surgery. The correlation between a history of metal reactivity and positive patch tests to metals is from 70 to 80%. Although there are case reports of patients with documented sensitization to nickel or cobalt who tolerate implants containing those metals without problems, as yet we have no means of identifying which patients are at risk of developing adverse reactions post-surgery and which are not. To be able to do so would greatly simplify the decision of who to test and which implant to use. Although there are no randomized prospective studies of the outcome of metal allergic patients assigned to implants with or without the allergenic metal in question, a number of studies demonstrate that those with an implant selected to avoid the metal in question do well. Since the average rate of implant failure is about 10%, of which implant allergy constitutes a significant portion, these results suggest that choosing an implant based on allergy testing will associate with a good result. Other relevant history directing pre-operative testing includes skin burning, swelling, itching, or erosion to artificial nails (containing ethyl or methyl methacrylate), dental implants, dentures, or skin glue (which contain various cyanoacrylates). Because topical antibiotics can be added to bone cement, and also to surgical irrigation fluid, one can ask about skin reactions to Bacitracin, Neomycin, Neosporin®, or Polymixin.

The other group of orthopedic patients who should be tested for metal, bone cement, and antibiotic allergies are post implantation patients with failure, when the common causes of infection or mechanical mismatch have been ruled out. The goal is that any revision should be the last revision, given the difficulties of revision surgery, the reduced possibility of an excellent outcome, and the limited amount of bony revision that is possible. Making sure that the next implant is non-allergenic to the patient is critical to avoiding further revisions.

Table 5 Common implant components by manufacturer

			Components			
Manufacturer	Joint	Implant	Co/Cr	Ti alloy (Ti/Al/V)	Stainless steel	Other
1. Arthrex	Ankle	Screws, locking plate			X	
	Shoulder	Suture anchors		X		
	Foot	Screws, washers		X		
2. Biomet	Hip	Acetabular shell		X		
		Acetabular liner				UHMWPE
		Taperloc stem		X		
		Biolox Delta Option femoral head				Ceramic
		Ceramic head adaptor		X		
	Knee	Vanguard femoral	X			
		Vanguard femoral stems, screws		X		
		Microfixation femur	X			
		Vanguard microfixation tibial tray	X			
		Tibial bearings, patella				UHMWPE
		Custom HA femur, tibial tray		X	Hydroxyapatite coating	
		Oxford twin peg femur, tibial tray	X			
	Shoulder	Humeral head, glenosphere baseplate, screws, tray		X		
		Reverse glenoid	X			
3. DePuy	Hip	Trilok femoral stem		X		
		Summit Cemented stem	X			
		Summit uncemented stem		X		
		Summit tapered hip stem w/ porocoat		X		
		Summit Articuleze metal on metal (MOM) femoral head	X			
		Corail cementless stem		X		
		Prodigy cementless femoral stem	X			
		Pinnacle Gription acetabular shell		X		
		Pinnacle Sector II acetabular cup		X		
		Pinnacle metal insert	X			
		Acetabular insert				Ceramic
		Apex hole eliminator		X		
		S-ROM proximal sleeve, femoral stem		X		
		S-ROM MOM femoral head	X			
	Knee	Attune femoral posterior stabilized, tibial base	X			
		Universal fluted tibial stem		X		
		PFC Sigma femoral stem bolt	X			
		PFC Sigma tibial tray	X			
		PFC Sigma fluted femoral stem		X		
		PFC Sigma PS femoral augment	X			
		LCS PFJ trochlear insert	X			
		Sigma femoral adaptor, bolt	X			
		Sigma TC3 femur, femoral augment	X			
		Femoral offset stem bolt	X			
		Universal porous femoral sleeve		X		
		DePuy Sigma Total Condylar III Femoral Component	X			
		Genesis II femur				Zr/Niobium
		Genesis II tibial base plate		X		
		Synthes tibial plate, locking screw, cannulated screw			X	
		Femoral component	X			
	Shoulder	Global advantage humeral system	X			
		Global advantage humeral head		X		
		Global advantage humeral stem	X			
	Cervical spine	Synthes Vectra-One Plate, screw		X		
	Foot	Synthes MTP plate, screws			X	
4. Stryker	Hip	Trident acetabular cup		X		
		Exeter stem			X	
		Accolade TMZF stem		X		
		Femoral heads	X			Biolox ceramic
		V40 Alumina femoral head				Ceramic
	Knee	Biotech femoral component Accolade		X		
		Biotech Biolox femoral head			Alumina ceramic	
		Femoral components, augment	X			
		Triathlon femoral component, tibial baseplate	X			
		Rejuvenate SPT modular neck, stem	X			

Table 5 (continued)

			Components			
Manufacturer	Joint	Implant	Co/Cr	Ti alloy (Ti/Al/V)	Stainless steel	Other
		Femoral head C-Taper	X			
		MAKO femoral component	X			
		MAKO tibial baseplate		X		
	Foot/ ankle	Howmedica screws		X		
		Biotech tubular plate, screw			X	
	Arm	Cortical screws, compression plate			X	
5. Zimmer	Hip	Continuum Trilogy femoral component	tantalum trabecular metal: Fe, tungsten, moly, silicon, Ni, tantalum			
		Continuum Trilogy Acetabular System Trabecular Porous Shell		Ti alloy with tantalum coating (tungsten, moly, Ni, tantalum)		
		Continuum cluster hole cup		X	Tantalum trabecular metal	
		Femoral stem neck taper		X		
		Versys Hip system femoral head	X			
		Biolox Delta Alumina ceramic femoral head			Aluminum oxide	
	Knee	Persona screws			X	
		NexGen femur	X			
		NexGen tibial component		X		
		NexGen tibial cone	Tantalum trabecular metal (tungsten, moly, Ni)			
		NexGen LPS flex GSR femoral component	X			
		NexGen femoral component	X			
		Persona tibial components		X		
		Persona femur	X			
		Persona female hex screw, mix quad-sparing screw			X	
		Unicompartmental knee system femoral	X			
		Unicompartmental knee system tibial		X		
	Shoulder	Humeral stem, glenoid			Tantalum trabecular metal	
	Elbow	Humeral, ulnar component		X		
6. Wright	Hip	Conserve PlusA cup shell, femoral head	X			
		Perfecta cementless femoral stem	X			
		Profemur Renaissance modular stem, neck		X		
		Profemur modular neck		X		
		Conserve femoral head	X			
7. Smith & Nephew	Hip	Birmingham BHR femoral head, acetabular cup	X			
	Knee	Genesis II tibial tray		X		
		Legion PS Oxinium femoral component		Zirconium, niobium, chromium, hafnium, tin		
		Legion screw-on femoral L-wedge	X			
		Legion tibial tray, wedge, press-fit stem		X		
8. Aesculap	Knee	Vega femoral component, tibial plateau	X			
		Columbus femur	X			
9. Medacta	Hip	Acetabular shell			High nitrogen stainless steel	
	MectaCer femoral head ceramic cementless			X		
	Quadra-H femoral stem, porous coating					
	Knee	Evolis femoral component	X			
		Evolis tibial component		X		
		GMK femoral/tibial	X			
		Evolis screws, extension stems		X		
		GMK femoral wedge			X	
		GMK revision tibial augmentation			X	
		GMK primary femoral component	X			
		GMK primary tibial tray	X			
		GMK primary tibial insert, resurfacing patella				UHMWPE

The following are useful questions to help determine if an implant allergy is possible, and patch testing is indicated.

- Do you develop a red, itchy rash with or without tiny vesicles, swelling, or purulent drainage to metal earrings, necklaces, bracelets, watches, jean snaps, bra snaps, suspenders, or other metal objects touching your skin? (Note: contact with metal causing the skin to turn green or black, or stopping watches when worn, does not count as suggestive of an allergy.)
- Have you developed itching, oozing, swelling, or skin erosion next to artificial nails, or skin glue such as DermaBond®, Indermil®, Histoacryl®, or other skin glues?

Table 6 Selected reviews of sensitization to surgical implants

1. Schalock PC, Menne T, Johansen JD, Taylor JS, Maibach HI, Liden C, Bruze M, and JP Thyssen. Hypersensitivity reactions to metallic implants—diagnostic algorithm and suggested patch test series for clinical sue. Contact Dermatitis 2011;66:4–19.
2. Thyssen JP, Menne T, SChalock PC, Taylor JS, and HI Maibach. Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. Br J Dermatol 2011;164:473–8.
3. Basko-Plluska JL, Thyssen JP, and PC Schalock. Cutaneous and systemic hypersensitivity reactions to metallic implants. Dermatitis 2011;22(2): 65–79.
4. Thomas P and B Summer. Diagnosis and management of patients with allergy to metal implants. Expert Rev. Clin Immunol 2015;11(4):501–9.
5. Pacheco KA. Allergy to surgical implants. J Allergy Clin Immunol Pract. 2015;3(5):683–95.

- Can you use topical antibiotics such as Bacitracin or Neosporin® without developing a red, itchy rash?

If the answer is yes to any question, then the patient should undergo patch testing for implant allergy.

Patch Test Panels: Table 3 (Orthopedic Implants) and Table 4 (Cardiovascular/Surgical Implants)

Patch testing should be tailored to the implant in question, with the addition of extracts that address possible metal substitutes. There is no indication to use the same patch test panels for orthopedic implants and pacemakers, for example, since gold, platinum, and iridium are not relevant for orthopedic implants and gold has the potential to cause long-lasting reactions that are not clinically relevant. I recommend using duplicates of different metals, as many of these patch test allergens are not validated, and it is not clear if a specific metal salt makes a difference in diagnostic accuracy. Some extracts are irritants as well, including benzoyl peroxide and some metal chloride salts [61], which should be kept in mind in interpreting responses. I also advocate patch testing to actual bone cement, in part due to the known variability in concentration of acrylate extracts [62] and loss of potency of methacrylate extracts over time [63].

Sources of Extracts

Extracts can be purchased from only a few companies (Dormer, Smart Practice), of which only one, Smart Practice, is based in the USA. Unfortunately, only the allergens embedded in the True Test (Thin Layer Rapid Use Epicutaneous Patch Test) have been validated for irritancy and potency. Using extracts from different sources may help increase sensitivity of testing, although results always must be interpreted in the clinical context of the patient.

Alternative Testing Options

Patch testing remains the method of choice in identifying surgical implant allergies. There are some commercially available blood tests, based on the lymphocyte proliferation test, some of which have been validated against patch testing [64]. Limitations for these include availability only in specialized centers, undetermined correlation with patch test results, need for rapid handling of specimens, and unknown association of positive results with implant failure.

Interpretation of Results: Table 5 (Common Implant Components by Manufacturer)

One of the roles of the allergist is to provide an interpretation of the test results to the referring surgeon. To do so for the post-operative patient with joint failure requires that the consulting allergist obtain the surgical record with the sticker sheet in order to compare the implanted components to the patch test responses. The sticker sheet will identify the manufacturer, the identifying number of the implant type, and the particular lot number. Table 5 is a partial list of the alloys used in different surgical implants, but of necessity cannot include every available implant. The patch test responses must be matched to the implant components, in order to determine if an allergy is relevant and could contribute to the joint failure the allergist has been asked to evaluate. Further information about a specific implant can be obtained by calling the manufacturer's local representative, which the surgeon's office can provide. The operative report will indicate if bone cement was used and if antibiotics were added to the bone cement or to surgical irrigation fluid. Although antibiotics are unlikely to cause long-term joint failure, they can cause short-term pain and inflammation that can be easily avoided. In general, most knee implants are cemented, but most hip implants, especially in the USA, are not. Some shoulder implants, particularly reverse shoulders, also require the use of bone cement.

Summary Recommendations

Sensitization to surgical implant components encompasses metals, methyl methacrylate, and antibiotics. The largest affected group includes patients with orthopedic implants,

with a less extensive literature regarding patients with allergy to endovascular and neurosurgical implants. In general, patients with a reasonable prior history of reactivity to metal, methacrylates, or topical antibiotics, should undergo pre-implant testing that includes both the materials in question and alternates that could be used in their place. For post-implant patients, patch testing to implant components to document specific sensitization and help select alternatives is indicated once more common causes of implant failure, principally infection, or mechanical issues of size, shape, orientation, shifting, etc., have been ruled out. Working with the surgeon, the allergist or dermatologist can provide an important service in helping to select the proper implant components that will help ensure an impeccable outcome. For more and other information, Table 6 lists some other recent, excellent reviews of hypersensitivity reactions to surgical implants.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Cram P, Lu X, Kaboli PJ et al (2011) Clinical characteristics and outcomes of Medicare patients undergoing total hip arthroplasty, 1991–2008. JAMA 305:1560–1567
2. Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR (2012) Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. JAMA 308:1227–1236
3. Maradit Kremers H, Larson DR, Crowson CS et al (2015) Prevalence of total hip and knee replacement in the United States. J Bone Joint Surg Am 97:1386–1397
4. Ibrahim SA, Kim H, McConnell KJ (2016) The CMS comprehensive care model and racial disparity in joint replacement. JAMA 316:1258–1259
5. Hawker GA, Badley EM, Croxford R et al (2009) A population-based nested case-control study of the costs of hip and knee replacement surgery. Med Care 47:732–741
6. Rasanen P, Paavolainen P, Sintonen H et al (2007) Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. Acta Orthop 78:108–115
7. Daigle ME, Weinstein AM, Katz JN, Losina E (2012) The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. Best Pract Res Clin Rheumatol 26:649–658
8. Nwachukwu BU, Bozic KJ, Schairer WW et al (2015) Current status of cost utility analyses in total joint arthroplasty: a systematic review. Clin Orthop Relat Res 473:1815–1827
9. AAOS (2017) American Academy of Orthopaedic Surgeons (AAOS) to launch family of orthopaedic registries. http://newsroom.aaos.org/media-resources/news/american-academy-of-orthopaedic-surgeons-aaos-to-launch-family-of-orthopaedic-registries.htm#/search/aaos18/contact_type_id/14763690. Accessed 01/22/2018.
10. Ong KL, Mowat FS, Chan N, Lau E, Halpern MT, Kurtz SM (2006) Economic burden of revision hip and knee arthroplasty in Medicare enrollees. Clin Orthop Relat Res 446:22–28
11. Labek G, Thaler M, Janda W, Agreiter M, Stockl B (2011) Revision rates after total joint replacement: cumulative results from worldwide joint register datasets. J Bone Joint Surg (Br) 93:293–297
12. Labek G, Todorov S, Iovanescu L, Stoica CI, Bohler N (2013) Outcome after total ankle arthroplasty-results and findings from worldwide arthroplasty registers. Int Orthop 37:1677–1682
13. Dummit LA, Kahvecioglu D, Marrufo G et al (2016) Association between hospital participation in a Medicare bundled payment initiative and payments and quality outcomes for lower extremity joint replacement episodes. JAMA 316:1267–1278
14. Sharkey PF, Lichstein PM, Shen C, Tokarski AT, Parvizi J (2014) Why are total knee arthroplasties failing today—has anything changed after 10 years? J Arthroplast 29:1774–1778
15. Jafari SM, Coyle C, Mortazavi SM, Sharkey PF, Parvizi J (2010) Revision hip arthroplasty: infection is the most common cause of failure. Clin Orthop Relat Res 468:2046–2051
16. Delaunay C, Hamadouche M, Girard J, Duhamel A (2013) So FG. What are the causes for failures of primary hip arthroplasties in France? Clin Orthop Relat Res 471:3863–3869
17. Evans EM, Freeman MA, Miller AJ, Vernon-Roberts B (1974) Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. J Bone Joint Surg (Br) 56-B: 626–642
18. Elves MW, Wilson JN, Scales JT, Kemp HB (1975) Incidence of metal sensitivity in patients with total joint replacements. Br Med J 4:376–378
19. Thienpont E, Berger Y (2013) No allergic reaction after TKA in a chrome-cobalt-nickel-sensitive patient: case report and review of the literature. Knee Surg Sports Traumatol Arthrosc 21:636–640
20. Granchi D, Cenni E, Trisolino G, Giunti A, Baldini N (2005) Sensitivity to implant materials in patients undergoing total hip replacement. J Biomed Mater Res B Appl Biomater 77:257–264
21. Krecisz B, Kiec-Swierczynska M, Chomiczewska-Skora D (2012) Allergy to orthopedic metal implants—a prospective study. Int J Occup Med Environ Health 25:463–469
22. Eben R, Dietrich KA, Nerz C et al (2010) Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty. Dtsch Med Wochenschr 135:1418–1422
23. Atanaskova Mesinkovska N, Tellez A, Molina L et al (2012) The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants. Arch Dermatol 148:687–693
24. Thomas P, Braathen LR, Dorig M et al (2009) Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. Allergy 64:1157–1165
25. Treudler R, Simon JC (2007) Benzoyl peroxide: is it a relevant bone cement allergen in patients with orthopaedic implants? Contact Dermatitis 57:177–180
26. Edwards SA, Gardiner J (2007) Hypersensitivity to benzoyl peroxide in a cemented total knee arthroplasty: cement allergy. J Arthroplast 22:1226–1228
27. Bircher A, Friederich NF, Seelig W, Scherer K (2012) Allergic complications from orthopaedic joint implants: the role of delayed hypersensitivity to benzoyl peroxide in bone cement. Contact Dermatitis 66:20–26
28. Haddad FS, Cobb AG, Bentley G, Levell NJ, Dowd PM (1996) Hypersensitivity in aseptic loosening of total hip replacements. The role of constituents of bone cement. J Bone Joint Surg (Br) 78:546–549
29. Erpenbach J, Hofmeister E (2008) Hypersensitivity to polymethylmethacrylate following shoulder hemiarthroplasty. Orthopedics 31:708
30. Anand A, McGlynn F, Jiranek W (2009) Metal hypersensitivity: can it mimic infection? J Arthroplast 24:826 e825–826 e828

31. Willert HG, Buchhorn GH, Fayyazi A et al (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 87: 28–36
32. Thomas P, von der Helm C, Schopf C et al (2015) Patients with intolerance reactions to total knee replacement: combined assessment of allergy diagnostics, periprosthetic histology, and periimplant cytokine expression pattern. Biomed Res Int 2015:910156
33. Mahendra G, Pandit H, Kliskey K, Murray D, Gill HS, Athanasou N (2009) Necrotic and inflammatory changes in metal-on-metal resurfacing hip arthroplasties. Acta Orthop 80:653–659
34. Koster R, Vieluf D, Kiehn M et al (2000) Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet 356:1895–1897
35. Saito T, Hokimoto S, Oshima S, Noda K, Kojyo Y, Matsunaga K (2009) Metal allergic reaction in chronic refractory in-stent restenosis. Cardiovasc Revasc Med 10:17–22
36. Banerji A, Lax T, Guyer A, Hurwitz S, Camargo CA Jr, Long AA (2014) Management of hypersensitivity reactions to Carboplatin and Paclitaxel in an outpatient oncology infusion center: a 5-year review. J Allergy Clin Immunol Pract 2:428–433
37. Pfoch L, Mahler V, Sticherling M (2009) Drug-eluting coronary stents: hypersensitivity reactions to paclitaxel. A case report. Dermatology 218:52–55
38. Nakazawa G (2011) Stent thrombosis of drug eluting stent: pathological perspective. J Cardiol 58:84–91
39. Svedman C, Moller H, Gruvberger B et al (2014) Implants and contact allergy: are sensitizing metals released as haptens from coronary stents? Contact Dermatitis 71:92–97
40. Halwani DO, Anderson PG, Lemons JE, Jordan WD, Anayiotos AS, Brott BC (2010) In-vivo corrosion and local release of metallic ions from vascular stents into surrounding tissue. J Invasive Cardiol 22:528–535
41. Svedman C, Ekqvist S, Moller H et al (2009) A correlation found between contact allergy to stent material and restenosis of the coronary arteries. Contact Dermatitis 60:158–164
42. Thyssen JP, Engkilde K, Menne T, Johansen JD, Hansen PR, Gislason GH (2011) No association between metal allergy and cardiac in-stent restenosis in patients with dermatitis—results from a linkage study. Contact Dermatitis 64:138–141
43. Gimenez-Arnau A, Riambau V, Serra-Baldrich E, Camarasa JG (2000) Metal-induced generalized pruriginous dermatitis and endovascular surgery. Contact Dermatitis 43:35–40
44. Guerra A, Kirkwood M (2017) Severe generalized dermatitis in a nickel-allergic patient with a popliteal artery nitinol stent. J Vasc Surg Cases Innov Tech 3:23–25
45. Jetty P, Jayaram S, Veinot J, Pratt M (2013) Superficial femoral artery nitinol stent in a patient with nickel allergy. J Vasc Surg 58: 1388–1390
46. D'Arrigo G, Giaquinta A, Virgilio C, Davi A, Pierfrancesco V, Veroux M (2014) Nickel allergy in a patient with a nitinol stent in the superficial femoral artery. J Vasc Interv Radiol 25:1304–1306
47. Khan SF, Sherbondy MA, Ormsby A, Velanovich V (2007) Occlusion of metallic biliary stent related to nickel allergy. Gastrointest Endosc 66:413–414
48. Prestipino F, Pragliola C, Lusini M, Chello M (2014) Nickel allergy induced systemic reaction to an intracardiac amplatzer device. J Card Surg 29:349–350
49. Spina R, Muller DW, Jansz P, Gunalingam B (2016) Nickel hypersensitivity reaction following Amplatzer atrial septal defect occluder device deployment successfully treated by explantation of the device. Int J Cardiol 223:242–243
50. Rigatelli G, Cardaioli P, Giordan M et al (2007) Nickel allergy in interatrial shunt device-based closure patients. Congenit Heart Dis 2:416–420
51. Kang J, Simpson CS, Campbell D et al (2013) Cardiac rhythm device contact dermatitis. Ann Noninvasive Electrocardiol 18:79–83
52. Citerne O, Gomes S, Scanu P, Milliez P (2011) Painful Eczema mimicking pocket infection in a patient with an ICD: a rare cause of skin allergy to nickel/cobalt alloy. Circulation 123:1241–1242
53. Andrews ID, Scheinman P (2011) Systemic hypersensitivity reaction (without cutaneous manifestations) to an implantable cardioverter-defibrillator. Dermatitis 22:161–164
54. Abdallah HI, Balsara RK, O'Riordan AC (1994) Pacemaker contact sensitivity: clinical recognition and management. Ann Thorac Surg 57:1017–1018
55. Delaplace M, Maitre F, Dufour T et al (2010) Two cases of cutaneous erythema following spinal cord stimulation. Ann Dermatol Venereol 137:297–300
56. Taverner MG (2013) A case of an allergic reaction to a spinal cord stimulator: identification of the antigen with epicutaneous patch testing, allowing successful reimplantation. Neuromodulation 16: 595–599
57. Schmidlin K, Verzwyvelt J, Bernstein D, Kim H (2015) Probable delayed-type hypersensitivity to nickel-containing cerebral aneurysm clip associated with neurologic deficits. J Allergy Clin Immunol Pract 3:609–611
58. Gautschi OP, Schlett CL, Fournier JY, Cadosch D (2010) Laboratory confirmed polymethyl-methacrylate (Palacos)-hypersensitivity after cranioplasty. Clin Neurol Neurosurg 112:915–916
59. King L Jr, Fransway A, Adkins RB (1993) Chronic urticaria due to surgical clips. N Engl J Med 329:1583–1584
60. Fage SW, Muris J, Jakobsen SS, Thyssen JP (2016) Titanium: a review on exposure, release, penetration, allergy, epidemiology, and clinical reactivity. Contact Dermatitis 74:323–345
61. Keane FM, Morris SD, Smith HR, Rycroft RJ (2001) Allergy in coronary in-stent restenosis. Lancet 357:1205–1206 author reply 1206–1207
62. Goon AT, Bruze M, Zimerson E et al (2011) Variation in allergen content over time of acrylates/methacrylates in patch test preparations. Br J Dermatol 164:116–124
63. Goon AT, Bruze M, Zimerson E et al (2011) Correlation between stated and measured concentrations of acrylate and methacrylate allergens in patch-test preparations. Dermatitis 22:27–32
64. Pacheco K, Barker L, Maier L, Erb S, Sills M, Knight V (2013) Development of a validated blood test for nickel sensitization. J Allergy Clin Immunol 132:767–769