REVIEW ARTICLE

CURRENT CONCEPTS

Treatment of Infections Associated with Surgical Implants

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ABOUT HALF OF THE 2 MILLION CASES OF NOSOCOMIAL INFECTION THAT occur each year in the United States are associated with indwelling devices. Although less common than infections related to catheters, infections associated with surgical implants are generally more difficult to manage because they require a longer period of antibiotic therapy and repeated surgical procedures.[1,2] In 2002, the Multidisciplinary Alliance against Device-Related Infections (www.maadrialliance.org) was established to organize groups of experts to develop guidelines for treatment. The four objectives of this review of infections associated with a variety of surgical implants are to describe the clinical and economic effects, address diagnostic challenges, discuss the general principles of medical and surgical treatment, and analyze implant-specific therapeutic approaches.

CLINICAL AND ECONOMIC CONSEQUENCES

Infections that are associated with a variety of surgical implants have clinical and economic consequences (Table 1). Mortality attributable to such infections is highest among patients with cardiovascular implants, particularly prosthetic heart valves and aortic grafts. Infections associated with orthopedic devices and ventricular shunts often result in serious disabilities. Although infections of mammary and penile implants are rarely life-threatening, they can cause major disfigurement and psychological trauma. The average rates of infection listed in Table 1 are for initially inserted implants, which are less likely than replacement implants to become infected.[2] The nature and the number of stages of surgical intervention vary according to the type of implant. Except for combination pacemaker–defibrillator systems, the cost of an implant itself usually constitutes a small fraction of the overall cost of treating implant-associated infections.

DIAGNOSTIC CHALLENGES

Some, but not all, postoperative wound infections affect the surgical implant.[2,1] However, bacterial colonization of surgical implants does not necessarily indicate infection. In fact, most colonized implants do not become infected. The ultimate proof of implant-associated infection requires the presence of clinical manifestations, intraoperative signs of infection adjacent to the implant, and the growth of pathogens in cultures of surgical specimens. To help obviate the need to operate on a patient who may not have an implant-associated infection, one can rely on certain microbiologic and imaging studies that are implant-specific. Although bacteremia is the hallmark of prosthetic-valve endocarditis and some infections associated with vascular grafts, blood cultures are negative in most cases of infection associated with pacemaker–defibrillator systems (unless endocarditis is present), ventricular assist devices, orthopedic devices, ventricular shunts, mammary implants, and penile implants.

Table 1. Clinical and Economic Consequences of Infections Associated with Surgical Implants.*

Implant	Implants Inserted in the U.S. Annually	Projected Infections of Implants Annually	Average Rate of Infection†	Preferred Practice of Surgical Replacement	Estimated Average Cost of Combined Medical and Surgical Treatment
	no.		%	*no. of stages*	*U.S. $*
Cardiovascular					
Mechanical heart valve	85,000	3,400	4	1	50,000
Vascular graft‡	450,000	16,000	4	1 or 2	40,000
Pacemaker–defibrillator	300,000	12,000	4	2	35,000§
Ventricular assist device	700	280	40	1	50,000
Orthopedic					
Joint prosthesis	600,000	12,000	2	2	30,000
Fracture-fixation device¶	2,000,000	100,000	5	1 or 2	15,000
Neurosurgical — ventricular shunt	40,000	2,400	6	2	50,000
Plastic — mammary implant (pair)	130,000	2,600	2	2	20,000
Urologic — inflatable penile implant	15,000	450	3	2	35,000

* The information is from published studies,[2-20] market reports, and data provided by medical and surgical organizations, physicians, and device-manufacturing companies. The average costs reflect the usual charges by private institutions (taking into consideration that portions of the antibiotic courses, particularly prolonged courses, are sometimes administered in an outpatient setting) and exclude loss of income because of infection.

† The average rate of infection refers to initially inserted implants, which are less likely to become infected than replacement implants.[2] For mechanical heart valves, the average rate refers to the incidence of prosthetic-valve endocarditis within 60 months after implantation.[3,4] For ventricular assist devices, it refers to infections documented within three months after implantation,[10,11] and for ventricular shunts, it refers to infections in adults and children, even though children are more likely to become infected.[17,18]

‡ The average rate of infection of vascular grafts refers to arteriovenous, femoropopliteal, and aortic grafts combined.[5-7] The average cost of treatment refers to infections associated with all three types of vascular grafts.

§ The average cost of treatment represents a weighted average of the costs of treating infections of pacemakers ($25,000) and pacemaker–defibrillator systems ($50,000)[9]; the difference in the cost of treating infections of these two systems is largely attributed to the difference in the average cost to a hospital of a pacemaker ($5,000) and a pacemaker–defibrillator system ($30,000).

¶ Fracture-fixation devices include intramedullary nails, external-fixation pins (which are more likely to become infected than intramedullary nails), plates, and screws. A one-stage procedure is usually performed in patients with bone union, and a two-stage procedure in the absence of bone union. The average cost of treatment refers to infections associated with the various types of fracture-fixation devices. Treatment of infections of intramedullary nails is more expensive than treatment of infections of external-fixation pins (average costs, $25,000 vs. $5,000).

Nonoperative cultures of local body fluids vary in their sensitivity for detecting infections associated with implants. For example, a culture of cerebrospinal fluid from a ventricular shunt has a sensitivity greater than 90 percent, whereas a culture of fluid from a prosthetic joint space, obtained by percutaneous aspiration, has a sensitivity of less than 50 percent. A transesophageal echocardiogram is much more sensitive than a transthoracic echocardiogram in identifying vegetations around prosthetic heart valves and pacemaker leads. Infection associated with vascular grafts can be diagnosed with computed tomographic (CT) scanning, magnetic resonance imaging (MRI), or, in the case of an aortoenteric fistula, esophagogastroduodenoscopy.[22] Since nuclear scans can yield false positive results up to a few months after surgical placement of orthopedic devices, CT and MRI scans are more reliable in diagnosing infection. Figure 1 shows some clinical, radiologic, and microscopical findings that can help in the diagnosis of implant-related infections.

GENERAL PRINCIPLES OF TREATMENT

The essential factor in the evolution and persistence of infection is the formation of biofilm around implanted devices.[23] Soon after insertion, a conditioning layer composed of host-derived adhesins (including fibrinogen, fibronectin, and collagen) forms on the surface of the implant and invites the adherence of free-floating (planktonic) organisms. Bacterial cell division, recruitment of additional planktonic organisms, and secretion of bacterial products (such as the glycocalyx) follow. A three-dimensional structure of biofilm finally evolves that contains

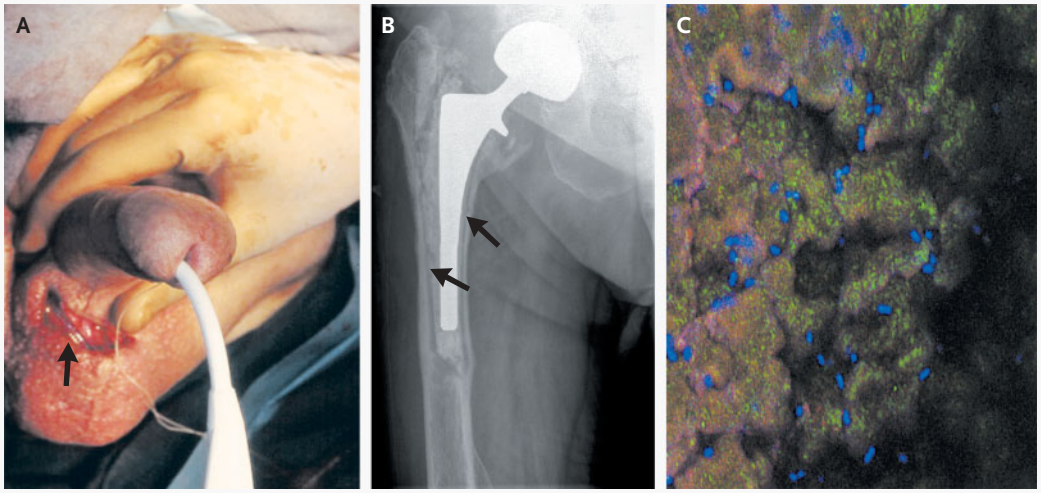

Figure 1. Clinical, Radiologic, and Microscopical Findings in Patients with Implant-Related Infections.

Panel A shows the clinical presentation of a penile implant that became infected with *Staphylococcus epidermidis* and eroded through the scrotum (arrow). (Photograph courtesy of Dr. Timothy Boone.) In Panel B, the roentgenographic finding of radiolucent lines (arrows) at the cement–bone interface around a hip prosthesis that had been implanted six months earlier raises the possibility of infection, which was confirmed by the intraoperative finding of purulent material around the hip implant. (Radiograph courtesy of Dr. Glenn Landon.) Panel C is a confocal scanning laser microscopical image of the biofilm surrounding a urologic device. It shows bacterial DNA (*Enterococcus faecalis*), stained blue (DRAQ5, ×1000), and carbohydrate material, stained green (SYTOX green, ×1000). (Image courtesy of Dr. Barbara Trautner.)

complex communities of tightly attached (sessile) bacteria. These bacteria display cell-to-cell signaling and exist within a polymer matrix containing fluid channels that allow for the flow of nutrients and waste.[24] Possible reasons for the reduced susceptibility of biofilm-embedded organisms to antibiotic agents, as compared with their free-floating counterparts, include a slow rate of bacterial growth within the biofilm, inhibition of antimicrobial activity by biofilm substances, and poor penetration of the biofilm by antibiotics.

The most important clinical objectives in treating infections associated with surgical implants are to cure the infection, prevent its recurrence, preserve body function, and reduce the risk of death. In most cases, these objectives can be achieved with both antibiotic therapy and surgical intervention. Table 2 summarizes the general principles of the medical and surgical treatment of infections that are associated with surgical implants. About two thirds of infections are caused by either *Staphylococcus aureus* or coagulase-negative staphylococci. Methicillin-resistant staphylococci are variably susceptible to older antibiotics (doxycycline, trimethoprim–sulfamethoxazole, quinolones, and clindamycin), and they are almost universally sensitive to the newer agent linezolid, but the clinical efficacy of these drugs for the treatment of infections associated with surgical implants has not been prospectively compared with the efficacy of vancomycin.

Most implants that are infected by *S. aureus* or candida require surgical removal (Table 2). Patients with an established response to medical therapy for an implant infection caused by the less virulent coagulase-negative staphylococci may not require surgery to remove the implant. If a decision is made to remove the infected implant, complete extraction of all components is essential, if surgically feasible, regardless of the type of infecting organism. Although surgical removal of the infected implant is generally associated with a better outcome than is retention of the infected implant, medical treatment alone may be warranted in patients who are at high risk for intraoperative or postoperative complications.

IMPLANT-SPECIFIC THERAPEUTIC APPROACHES

PROSTHETIC HEART VALVES

Although relatively uncommon, prosthetic-valve endocarditis is life-threatening, with mortality ex-

ceeding 30 percent.[4] Curing prosthetic-valve endocarditis may require a combination of antibiotic therapy and surgical intervention. Medical therapy consists of a six-week course of systemic bactericidal antibiotics. Bacteriostatic antibiotics, such as clindamycin, should not be used for the treatment of staphylococcal endocarditis. Although in-hospital mortality is generally higher among medically treated patients than among patients who undergo surgery (46 percent vs. 24 percent), this difference in mortality almost disappears when patients who are treated medically simply because they are considered to be too sick for curative treatment are excluded from the analysis.[25] However, a recurrence of endocarditis, which warrants surgery, is more likely in medically treated patients.[25] Patients with aortic paravalvular abscesses, particularly those caused by *S. aureus*, have a very poor prognosis when treated medically.[26]

Clinical practice dictates surgical replacement of almost all prosthetic valves infected by *S. aureus* or candida. Surgical intervention may not be required in patients infected by coagulase-negative staphylococci that have already responded to antibiotic therapy. Regardless of the causative pathogen, cardiac complications (e.g., congestive heart failure, conduction abnormalities, paravalvular abscesses, valve dehiscence, and serious peripheral embolization) necessitate the surgical replacement of the infected prosthesis. Since emergency surgery is associated with high mortality,[27] it is essential that surgery be performed before patients become hemodynamically unstable. Central nervous system complications may be aggravated by cardiopulmonary bypass and postoperative anticoagulation, and if valve replacement is indicated in patients with such complications, surgery is delayed for 10 days or even a few weeks, until their neurologic condition stabilizes.[3] Figure 2 shows the therapeutic quandary that may evolve in the context of surgical treatment of prosthetic-valve endocarditis due to *S. aureus*, a condition associated with high mortality.[3,28,29]

Patients with prosthetic heart valves receive long-term oral anticoagulant therapy, and it is prudent to consider a particular patient's circumstances in making decisions about when to stop anticoagulation before surgical replacement of the infected valve and when and at what dose to restart it postoperatively. Warfarin is usually stopped at least two days before nonemergency surgical replacement, but in the case of an emergency procedure, anticoagulation should be reversed rapidly with fresh-frozen plasma. Anticoagulation is usually reinitiated (typically at a dose lower than the preoperative dose, because of the postoperative depletion of coagulation factors) about four to seven days after surgery to reduce the risk of bleeding — a risk that is particularly high around the time of removal of the epicardial pacemaker (a few days postoperatively).

Table 2. General Principles of the Medical and Surgical Treatment of Infections Associated with Surgical Implants.

Principles of medical therapy
Do not use vancomycin in patients infected by methicillin-susceptible staphylococci, because this treatment is suboptimal.
Provide empirical coverage against methicillin-resistant staphylococci for infections with an unidentified microbiologic cause.
If the infected implant is retained or if the response to a single antimicrobial agent is inadequate, use combination antibiotic therapy that includes rifampin for staphylococcal infection.
When performing the second stage of implant replacement, provide antibiotic coverage against organisms isolated during the first surgery.
Administer long-term antibiotic therapy if a new implant is placed in a grossly infected area.
Principles of surgical therapy
Cure of infection is likely to require removal of implants infected by virulent organisms such as *Staphylococcus aureus* and candida, but removal may not be required in the case of infection by less pathogenic coagulase-negative staphylococci.
Regardless of the microbiologic cause of infection, remove the infected implant if the patient has not had a response to seemingly appropriate antibiotic therapy.
Remove all components of an infected implant to prevent a recurrence of infection.
Ensure the absence of clinical and, if necessary, microbiologic evidence of infection before embarking on the second stage of surgical replacement.

VASCULAR GRAFTS

The three major types of prosthetic vascular grafts (arteriovenous, femoropopliteal, and aortic) differ with regard to the associated rates of infection and the most pertinent complications.[30] More than 5 percent of arteriovenous grafts become infected, necessitating another means of access to ensure uninterrupted hemodialysis. Infection occurs in about 4 percent of femoropopliteal grafts and can result in limb loss. Although infection of aortic grafts is the least likely (the rate of infection is about 2 percent), this complication is lethal in almost 90 percent of cases.

A combination of medical and surgical treatment is used for most infected vascular grafts. The duration of antibiotic therapy is determined by the presence of septicemia (treated with systemic antibiotics for six weeks) or an abscess. Surgical inter-

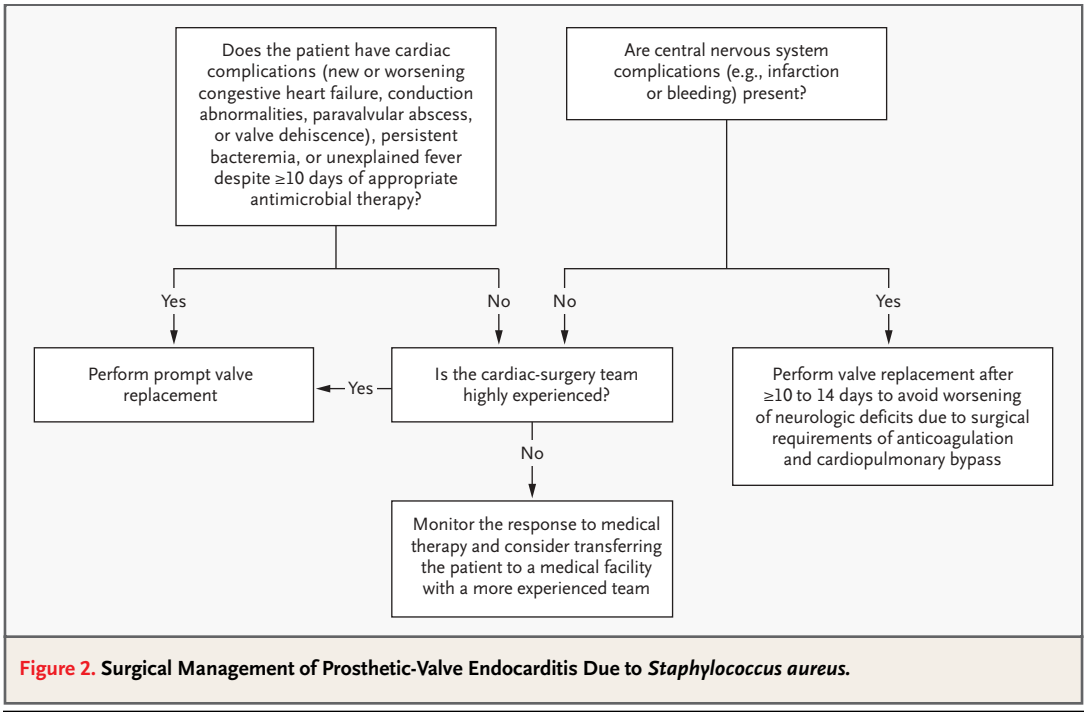

Figure 2. Surgical Management of Prosthetic-Valve Endocarditis Due to *Staphylococcus aureus*.

vention is tailored to the condition of the patient and the type of graft, and in many cases alternatives to traditional therapeutic approaches need to be considered.[5,31] Combined vascular reconstruction and adjunctive tissue transfer is often necessary in patients with tissue defects.

No prospective studies have compared the various surgical treatments of infections associated with different types of vascular grafts. Traditional treatment of infected arteriovenous grafts is performed in two stages: the infected graft is removed before a new polytetrafluoroethylene graft or fistula is placed elsewhere, with interim placement of a dialysis catheter until the new graft or fistula matures, in four to six weeks.[32] A new therapeutic approach that has recently been developed consists of inserting a new polyurethane graft that can be used immediately, thereby obviating the need for a temporary dialysis catheter. In patients with limited venous access, a one-stage procedure to remove the infected graft and replace it with a cryopreserved human allograft can be performed.[33] (The Food and Drug Administration has expressed concern about the validation of methods used to prevent microbial contamination of allograft tissue and has limited the distribution of some cryopreserved grafts, pending implementation of certain preventive procedures.) This approach to the treatment of infected grafts results in a relatively low incidence of reinfection and a rate of graft patency similar to that with the placement of prosthetic grafts.

Surgical management of infected femoropopliteal grafts usually consists of a one-stage procedure for graft excision and revascularization with autologous venous conduits, prosthetic grafts, or cryopreserved homografts.[34] In patients with a favorable risk–benefit ratio for surgical intervention, infections of aortic grafts are treated with either axillofemoral bypass grafting, followed by excision of the infected graft,[35] or graft excision plus in situ replacement with cryopreserved homografts,[7] autologous vascular conduits, or if the infecting organism has low virulence (such as coagulase-negative staphylococci), prosthetic grafts.[31]

PACEMAKER–DEFIBRILLATOR SYSTEMS

The combined medical and surgical treatment of infections of pacemakers is similar to that of pacemaker–defibrillator systems.[8,36] Patients with clinical infection of the pulse-generator pocket without bloodstream infection receive systemic antibiotics for 10 to 14 days, whereas patients with lead-associated endocarditis receive a 6-week course of systemic antibiotics. The mainstay of surgical management is a two-stage approach that consists initially of complete removal of the entire implanted system, including the cardiac leads (by means of laser-assisted extraction, if needed), even in patients with

clinical infection of only the pocket, because their cardiac leads may already be colonized. Although rare instances of curing the infection with antibiotics alone have been reported,[37] recurrence of infection is generally more likely in patients treated with antibiotics alone, or with antibiotics plus removal of only the generator, than in patients who undergo extraction of the whole system.[38] Before the new implant is placed, the cardiac rhythm can be controlled either by a temporary transvenous pacemaker (exchanged every 5 to 10 days) or by cardiac medications; patients with a history of ventricular fibrillation may wear an external defibrillator vest at home. The new implant is placed on the contralateral side as early as 10 to 14 days after removal of the implanted system in patients with infection of the pulse-generator pocket and as late as 6 weeks in those with endocarditis.

LEFT VENTRICULAR ASSIST DEVICES

In patients with left ventricular assist devices, infection can develop in the percutaneously placed drive line, the generator pocket, and the bloodstream.[39] Although potentially serious, these infections do not decrease the likelihood of successful transplantation.[40] Infection is often initiated by mechanical disruption of the interface between the tissue and the drive line and is manifested as drainage that may defy treatment with antibiotics alone and may require surgical excision or revision of the exit site. Since left ventricular assist devices are considered life-sustaining,[10] explanting or replacing the entire infected device before a heart becomes available for transplantation is a risky, if not impossible, option.

JOINT PROSTHESES

The four possible surgical approaches for the treatment of infected joint prostheses are débridement plus retention of the prosthesis, removal of the infected implant without replacement, one-stage replacement, and two-stage replacement.[13,14,41-44] The two-stage replacement approach results in higher cure rates and yields better function than one-stage replacement. In the first stage, the infected implant is removed and a biodegradable (polylactic acid or polyglycolic acid) or nonbiodegradable (polymethylmethacrylate) antimicrobial carrier is placed. After the patient completes a six-week course of systemic antibiotics, a new joint prosthesis is placed. In patients who have undergone multiple surgical procedures for the treatment of infection with particularly virulent organisms, arthrodesis may be necessary.

A single prospective, randomized, double-blind, placebo-controlled trial compared two treatment approaches, both intended to salvage the implant, in patients who had infections associated with joint prostheses or fracture-fixation devices.[16] Among patients who had a mechanically stable implant, whose symptoms had lasted three weeks or less, and who had undergone adequate surgical débridement, the cure rate with three to six months of systemic therapy with ciprofloxacin and rifampin was 100 percent, as compared with a 58 percent cure rate with ciprofloxacin and placebo. Since most failures in the placebo group were associated with the emergence of resistance to ciprofloxacin during therapy, combining rifampin with ciprofloxacin also helped provide protection against the evolution of ciprofloxacin resistance. The results of this trial[16] and other, differently designed studies[13,14,42,43] provide the basis for a therapeutic algorithm for the treatment of staphylococcal infections of joint prostheses (Fig. 3).

FRACTURE-FIXATION DEVICES

Infections of fracture-fixation devices that involve bone are treated with a 6-week course of systemic antibiotics, whereas 10 to 14 days of antibiotic therapy are sufficient for superficial infections. The nature of the surgical intervention in patients with infected fracture-fixation devices depends on the type of device, the presence or absence of bone union, and the patient's underlying condition.[45] Infection of intramedullary nails is often associated with nonunion of bone and requires removal of the infected nail, insertion of external-fixation pins, and if necessary, subsequent insertion of a replacement nail. Surgical treatment of infection of external-fixation pins usually consists of a single procedure to remove the infected pins and, if bone union has not occurred, either insert new pins at a distant site or fuse the bones. Attempts can be made to salvage infected fracture-fixation devices in carefully selected patients by using a prolonged course of systemic antibiotics[12,14,16,43] (Fig. 3).

VENTRICULAR SHUNTS

Infected ventricular shunts are surgically managed in two stages.[46] The infected shunt is removed, and an external ventricular catheter is contemporaneously inserted to drain cerebrospinal fluid and monitor intracranial pressure. The external ventricular catheter is usually replaced every 5 to 10 days to prevent ventriculitis,[47] and systemic antibiotics are given for 10 to 14 days. Repeated analysis of cerebro-

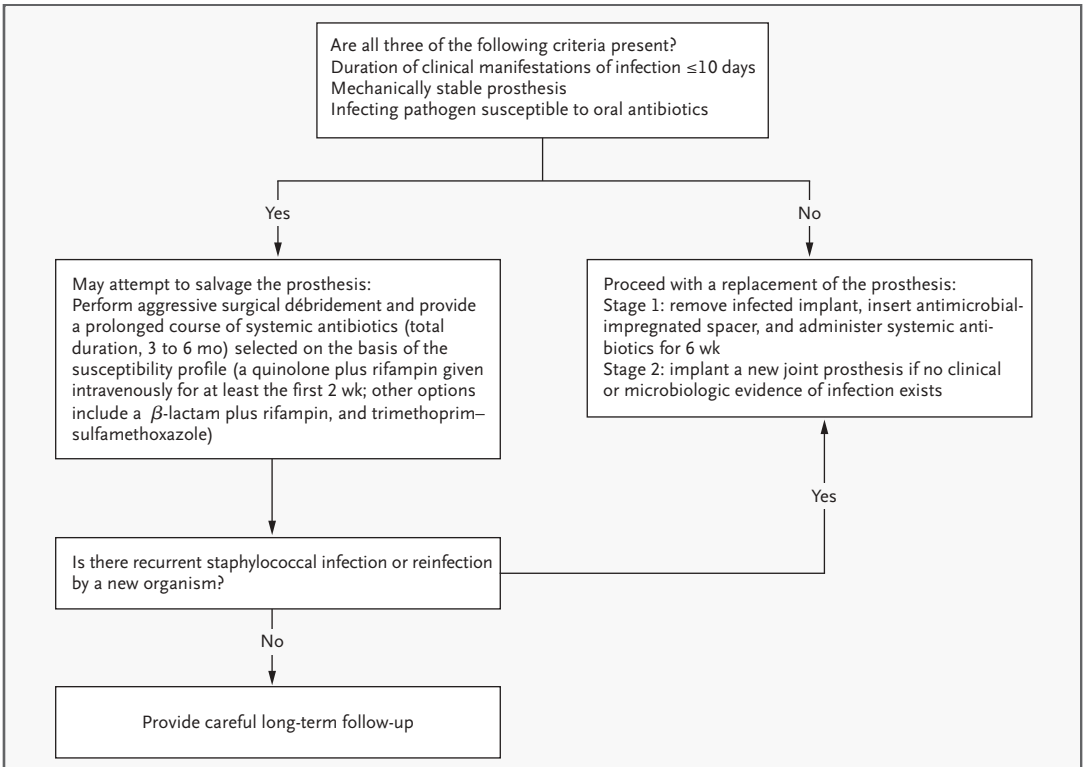

Figure 3. Management of Joint Prosthesis–Related Infection Caused by *Staphylococcus aureus* or Coagulase-Negative Staphylococci.

spinal fluid is performed to ensure sterility before a new ventricular shunt is inserted, preferably on the contralateral side and usually within two weeks after the initial surgery.[48]

MAMMARY IMPLANTS

Management of an infected mammary implant usually entails a two-stage replacement procedure.[19] The first surgery involves removal of the infected implant and débridement of the capsule surrounding it. A 10-to-14-day course of systemic antibiotics is administered to cover the infecting pathogen (or pathogens). A few months later, the contralateral implant is removed, and a new pair of mammary implants is inserted to replace the original pair and to achieve symmetry.

INFLATABLE PENILE IMPLANTS

There is a universal consensus on the need for surgical removal of infected penile implants. However, there are diverging views about the stages of surgical management. Although a single-stage replacement has been advocated for use in carefully selected patients,[49] the preferred approach is a two-stage replacement.[20] First, the infected implant is removed, and a malleable penile prosthesis is inserted to preserve space in the corpora cavernosa. For uncomplicated infections, a 10-to-14-day course of systemic antibiotics is given. Four to six months later, a new inflatable penile implant is inserted in place of the malleable prosthesis.

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