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Antimicrobial Approaches for Preventing Infections Associated with Surgical Implants

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Because management of infections associated with surgical implants can be both difficult and costly, prevention of such infections remains a priority. Preventive strategies comprise systemic perioperative administration of antibiotics and local application of antimicrobial agents (antibiotics or antiseptics). Local antimicrobial prophylaxis can be provided in various forms and aims to prevent implant-associated infections by impeding bacterial adherence to the implant surface and/or reducing the concentration of bacteria in the immediate vicinity of the implant. Analysis of the existing clinical practices and the pertinent medical literature indicates that, although some antimicrobial strategies constitute the standard of care for preventing infections associated with surgical implants, such strategies are often applied in a nonstandardized fashion and without clear evidence of clinical efficacy. This review article concludes with a perspective on assessing and preventing such serious infections.

Surgical implants constitute an essential component of modern medicine. The escalating use of both long-established and new surgical implants, particularly in patients inherently at high risk of infection, has magnified the clinical importance of infectious complications [1]. As with vascular and urinary catheters, infection is the most common serious complication associated with surgical implants. However, infections associated with surgical implants are generally more cumbersome to manage, have a greater adverse impact on quality of life, result in excessive prolongation of hospital stays, and incur higher costs [2, 3]. For instance, cure of infections associated with joint prostheses usually requires, in addition to a long course of systemic antibiotics, 2 surgical procedures to first explant the infected prosthesis and then, months later, to implant another prosthesis.

Over the last several years, we have witnessed major strides in the study of protective strategies and establishment of guidelines for the prevention of catheter-related infections [4]. Unfortunately, there has been much less focus on preventing infections associated with surgical implants. The objectives of this review article are as follows: (1) to address the limitations on assessing the clinical efficacy of strategies that can potentially prevent infections associated with surgical implants; (2) to assess the clinical efficacy of systemic and local antimicrobial preventive approaches; and (3) to provide perspective on assessing and preventing such infections.

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LIMITATIONS ON ASSESSING THE CLINICAL EFFICACY OF PREVENTIVE STRATEGIES

Prohibitively large size of sufficiently powered clinical trials. The major limitation on assessing the clinical efficacy of antimicrobial strategies for preventing infections associated with surgical implants is the prohibitively large size of sufficiently powered prospective, randomized clinical trials. Table 1 summarizes the estimated size of adequately powered clinical trials in relation to the level of reduction in the rate of infection (a large reduction of 50% vs. a moderate reduction of 25%). In general, larger numbers of patients would need to be studied for evaluation of surgical implants that have a relatively low baseline rate of infection, such as prosthetic heart valves [5], particularly if the experimental preventive strategy provides only moderate protection against infection. For instance, to confirm that an experimental antimicrobial strategy cuts by one-half the 2% baseline rate of prosthetic valve endocarditis, >5000 patients would need to be studied. Even more prohibitive

Table 1. Estimated size of prospective, randomized clinical trials required to sufficiently assess the efficacy of antimicrobial strategies for decreasing the infection rate associated with surgical implants.

		Preventive strategy, by anticipated reduction in infection rate[a]			
		50% reduction		25% reduction	
Infected implant	Baseline infection rate, %	New rate, %	Trial size[b]	New rate, %	Trial size[b]
Heart valve or joint prosthesis	2	1	5028	1.5	22,382
Penile implant	3	1.5	3328	2.25	34,378
CNS shunt	4	2	2478	3	10,998
Cardiac pacemaker	5	2.5	1968	3.75	8720
External fixation pin	10	5	948	7.5	4166
Left ventricular assist device	40	20	182	30	752

NOTE. $P = .05$, by Fisher's exact 2-sided test; power, 80%.

[a] Compared with the infection rate at baseline.

[b] Data are estimated number of patients in the trial.

would be the need to enroll >22,000 patients, if the studied preventive strategy is anticipated to result in only moderate reduction in the rate of endocarditis.

The unacceptably high cost (tens of millions of dollars) and great difficulty of accruing adequate numbers of patients (only 85,000 mechanical heart valves are inserted each year in the United States) prohibit the conduction of such large prospective, randomized clinical trials in the United States, as well as globally [1]. A similarly dim likelihood of conducting sufficiently powered clinical trials also applies for evaluation of some surgical implants that have a relatively high baseline rate of infection, such as left ventricular assist devices [6], although for a different reason. For example, although only 752 patients would need to be studied to confirm that a certain preventive strategy reduces the rate of infection associated with left ventricular assist devices from 40% to 30%, this number of patients exceeds the total number of such devices implanted in the United States per year (700) [1]. Although meta-analyses can theoretically provide a meaningful input on the efficacy of potentially preventive approaches, their conclusions are often limited by potential variations between analyzed studies with regard to study design, type and duration of antimicrobial intervention, definition of outcome, and duration of follow-up.

Paucity of data for replacement implants. The protective efficacy of antimicrobial approaches has been mostly examined in the context of preventing infection after first-time insertion of surgical implants. Although replacement surgical implants are more likely to become infected than are first-time implants, the much smaller number of replacement implants does not allow adequate evaluation of the clinical efficacy of preventive strategies. Another confounding factor that can limit the examination of anti-infective efficacy is the incomplete removal of all infected components of the surgical implant, as is the case with replacing the generator but not the wires of an infected pacemaker system [7].

Mischaracterization of postoperative infections as involving surgical implants. Most infections that occur after placement of surgical implants are superficial wound infections without involvement of deeper tissues and the adjacent indwelling implant (i.e., implant-associated infections). In some cases, implant-associated infection can be accurately suspected on the basis of clinical observations, microbiological data, and/or imaging findings. Although implant-associated infections can be confirmed only by surgical exploration and results of culture of the implant, this diagnostic approach has not been commonly adopted in clinical practice or in the research arena. An important drawback in the design of conducted clinical trials has been the underestimation of the study size, which has been based on the rates of surgical wound infections (which include both superficial and deep wound infections), rather than on the rates of implant-associated infections. The demonstrated ability of an antimicrobial approach to prevent surgical wound infection may not ensure that it also will specifically protect against implant-associated infection.

CLINICAL EFFICACY OF ANTIMICROBIAL APPROACHES

Both systemically administered and locally applied antimicrobial agents have been used with the objective of preventing infections associated with surgical implants. One advantage of systemic antibiotic prophylaxis is that it may provide activity against organisms that can disseminate via the bloodstream from a site distant from the surgical site, as in the case of a

patient with an intravascular catheter who undergoes heart valve replacement. In addition, systemic antimicrobial prophylaxis may protect against superficial wound infections. On the other hand, local applications of antimicrobial agents (antibiotics or antiseptics) usually provide higher drug levels on the surface of the device and/or in its immediate vicinity than do systemic administrations of antibiotics.

The clinical efficacy of preventive approaches is best assessed in a prospective, randomized clinical trial. Here, I address the results of only such designed studies that have been reported in peer-reviewed journals. Some, but not all, antimicrobial strategies have been proven to significantly protect against infections associated with surgical implants. Because of some differences between various types of surgical implants in terms of the microbiology of infection and the period of time it takes for indwelling implants to become covered with endothelial tissue (in the case of intravascular implants) or fibrotic tissue (in the case of extravascular implants), the clinical efficacy of a particular antimicrobial approach may differ among various implants.

The nature of the comparative arms differs between clinical trials that assess the clinical efficacy of systemic antimicrobial prophylaxis and those that evaluate local antimicrobial approaches. In the first group of studies, the experimental arm receives systemic antimicrobial drugs and the control arm receives placebo, whereas in the second group of studies, the experimental arm receives local *plus* systemic antimicrobial drugs and the control arm receives only systemic antimicrobial drugs.

SYSTEMIC ANTIBIOTIC PROPHYLAXIS

Only a few prospective, randomized clinical trials have demonstrated that systemic antibiotic prophylaxis significantly reduces the rate of infection after placement of surgical implants. As table 2 shows, the number of enrolled subjects constitutes the major determinant of the studies' abilities to successfully assess the impact of preventive strategies on the occurrence of implant-associated infection. Small studies showed a significant reduction only in the rate of surgical wound infections, along with a statistically insignificant trend toward a lower rate of implant-associated infections [8, 9], whereas the large Dutch Trauma Trial was capable of demonstrating significant reductions in the rates of both surgical wound infections and implant-associated infection [2]. Few small, prospective, randomized clinical trials that had, rather unexpectedly, reported a significant decrease in the rate of infections after placement of surgical implants were considered unreliable because of unclear definition of outcomes and/or excessively high rates of infection in the control arms and, therefore, were not included in table 2.

For some implants, such as cardiac pacemakers, none of the conducted prospective, randomized clinical trials was large enough to demonstrate the protective efficacy of systemic antimicrobial prophylaxis. However, a meta-analysis of 7 such studies that included a total of 2023 patients concluded that perioperative administration of antistaphylococcal antibiotics can significantly reduce infection by almost 4-fold (OR, 0.26; $P < .005$) [10]. The potential drawbacks of this meta-analysis include the variation in the type and duration of administration of antibiotics after implantation (range, 6 h–8 days).

Perioperatively administered antibiotics are usually chosen for their strong activity against staphylococci, the most common cause of infection associated with surgical implants. There exist no prospective comparative data on the clinical efficacy of cephalosporin (cefazolin or cefuroxime) or penicillin (nafcillin) compounds versus vancomycin for prevention of infections associated with surgical implants. However, the rising prevalence of methicillin-resistant *Staphylococcus aureus*, coupled with the fact that most coagulase-negative staphylococci are methicillin resistant, has prompted surgeons to increasingly use vancomycin for systemic prophylaxis. The antimicrobial spectrum of perioperative antibiotics is sometimes expanded to help prevent organisms residing at distant sites from hematogenously seeding the surgical implant, as may theoretically happen when implanting a joint prosthesis in a patient who

Table 2. Summary of selected prospective, randomized clinical trials that reliably demonstrated the efficacy of systemic antimicrobial prophylaxis versus that of placebo for preventing infection after placement of surgical implants.

				Infection rate in %, by type of surgical infection					
				Wound associated[a]			Implant associated		
Reference	No. of patients	Surgical implant	Antibiotic prophylaxis administered	Experimental arm	Placebo arm	*P*	Experimental arm	Placebo arm	*P*
Jensen et al. [8]	128	Vascular graft	Vancomycin	1.6	21.2	<.001	0	4.5	NS
Yerdel et al. [9]	280	Hernia mesh	Amp-Sulb	0.7	9	<.002	0.7	2	NS
Boxma et al. [2]	2195	Fracture fixator	Ceftriaxone	3.6	8.3	<.001	1.2	3.7	<.001

NOTE. Amp-Sulb, ampicillin-sulbactam; NS, not significant.

[a] Includes superficial and deep wound infections.

requires intraoperative placement of a Foley catheter into the bladder and the bladder contains gram-negative bacteria. Quite understandably, there exist no prospective comparative data about the potential additional protection afforded by including drugs active against gram-negative bacteria in the perioperative antibiotic regimen. However, observational studies indicate that perioperative bouts of clinical urinary tract infection, [11] but not asymptomatic bacteriuria [12], may be associated with infection of the implanted joint prostheses.

LOCAL ANTIBIOTIC PROPHYLAXIS

Bacterial colonization of the surgical implant is a prelude to clinical infection. Because most cases of implant-related infection that clinically manifest within 1 year of surgical placement are thought to result from perioperative inoculation of pathogens, the major purpose of local antibiotic prophylaxis is to prevent organisms from colonizing the implant and/or contaminating the tissues adjacent to the implant. The characteristics of the 4 major types of local antimicrobial prophylaxis are summarized in table 3. The first 2 approaches (antimicrobial irrigation of the surgical field and placement of antimicrobial carriers) are applied independently of the implant, whereas the last 2 approaches involve surface modification of the implant either intraoperatively (i.e., by dipping the implant in antimicrobial solution) *or* preoperatively (i.e., by coating the implant with an antimicrobial). The role of skin antisepsis will not be addressed in this review.

Antimicrobial irrigation of the surgical field. Although the clinical efficacy of this potentially preventive approach has not been demonstrated in a prospective, randomized clinical trial, this clinical practice constitutes a prevailing standard of care among surgeons of many specialties. The application of this approach is hampered by a number of variables, including volume and pressure of irrigation, nature of irrigation flow (i.e., pulsatile vs. constant), antimicrobial concentration in the irrigation solution, amount of locally available antimicrobial drugs (that either bind to the surgical implant or accumulate in its immediate vicinity), duration (usually <1 day) of local antimicrobial activity, and choice by individual surgeons of antimicrobial agents (frequently, vancomycin). The likelihood of detecting antimicrobial levels in serum depends on the location of the implant (the likelihood is greater with intravascular implants than with extravascular implants) and the total amount of applied antimicrobial agents (the likelihood is greater with larger amounts of applied antimicrobial drugs). For instance, intracavernous irrigation with gentamicin or neomycin at the time of placing penile implants results in nontoxic systemic levels of these antimicrobial agents, which gradually decline in a few hours [14].

Placement of antimicrobial carriers. Antimicrobial therapies can be incorporated in a carrier either preoperatively or during surgery. In a prospective, randomized, double-blind clinical trial of 595 patients, insertion of a gentamicin-treated collagen tampon adjacent to a polypropylene mesh used for repairing groin hernias was shown to reduce by >6-fold the rate of wound infections, as compared with the rate when no antimicrobial carrier was used (0.3% vs. 2%; $P = .04$) [15]; however, there were no specific data on the rate of prosthetic mesh–related infections. Impregnation of biodegradable polymers (polylactide or polygalactide) or nonbiodegradable polymers (polymethylmethacrylate) with antimicrobial drugs (usually aminoglycosides, which can tolerate the high temperatures generated during the exothermic process of formulating the cementing polymer) is often performed intraoperatively in patients with infected orthopedic prostheses. The mechanical properties of cement are usually not altered if the ratio of antibiotics to cement powder is <1 : 10. The clinical efficacy

Table 3. Comparison of locally administered antimicrobial therapies used to prevent infection associated with surgical implants.

Variable	Antimicrobial irrigation of surgical field	Placement of antimicrobial carrier	Dipping of implant in antimicrobial solution	Antimicrobial coating of implant
Established method of antimicrobial application	No	Yes/No[a]	No	Yes
Known amount of locally available antimicrobial[b]	No	No	No	Yes
Detectable antimicrobial levels in serum	Variable[c]	Unknown	Unlikely	Unlikely
Duration of local antimicrobial activity	<1 day	Weeks to months	Hours	Weeks to months
Utilizes drug(s) of choice	Surgeon dependent	Yes	Surgeon dependent	No
Demonstrated clinical efficacy[d]	No	No	Yes[e]	No

[a] Yes, for preoperatively prepared antimicrobial carriers; no, for intraoperatively assembled antimicrobial carriers.
[b] Locally available antimicrobials bind to the surgical implant or accumulate in the immediate vicinity of implant.
[c] The likelihood of detecting antimicrobial levels in serum varies on the basis of implant location (i.e., intravascular vs. extravascular) and total amount of applied antimicrobials.
[d] As demonstrated by significant reduction in the rate of implant-associated infection in a prospective, randomized clinical trial.
[e] Dipping of prosthetic heart valves has been evaluated in a single prospective, randomized clinical trial [13].

of this approach for preventing infections associated with orthopedic implants has not been demonstrated in a prospective randomized fashion. Neither the amount of locally available antimicrobial drugs nor the antimicrobial levels in serum are known. The local antimicrobial activity usually persists for weeks to months and is dependent on the rate of resorption of biodegradable carriers or on the timing of surgical removal of the nonbiodegradable carriers.

Dipping of implants in antimicrobial solutions. As with antimicrobial irrigation of the surgical field, the approach of dipping implants in antimicrobial solution has no established method of application and results in an undetermined amount of locally available antimicrobial drugs. However, the dipping approach incorporates relatively smaller amounts of antimicrobial drugs onto the surface of the implant, which explains the low likelihood for detecting systemic antimicrobial levels and the short duration (a few hours) of local antimicrobial activity. A single prospective, randomized clinical trial has reported significantly lower rates of prosthetic valve endocarditis associated with antibiotic-dipped (1.3%) versus undipped (5.4%) valves [16]. However, the study conclusions are limited by the large variety of administered antibiotics. Early results for 257 patients enrolled in a prospective, randomized clinical trial showed no significant advantages in the use of rifampin-dipped versus undipped vascular grafts, perhaps owing to the very low rate (~0.4%) of graft infection observed in that study [17].

Antimicrobial coating of implants. Compared with the other local antimicrobial approaches, the coating of surgical implants possesses the advantages associated with using an established method of antimicrobial application, knowing the amount of locally available antimicrobial drugs, having a low likelihood of detectable systemic antimicrobial levels, having a relatively persistent local antimicrobial activity lasting from weeks to months, and using a predetermined selection of nontherapeutic drug or drugs of choice. Such potential advantages, coupled with the variable clinical protection afforded by the antimicrobial coating of catheters, have magnified interest in the antimicrobial coating of surgical implants. The objective of this approach is to inhibit bacterial colonization of the implant and, it is hoped, to inhibit implant-associated infection. However, the protective efficacy of antimicrobial-coated surgical implants has yet to be demonstrated in a prospective, randomized clinical trial. Two such studies that involved the coating of external fixation pins [18] and prosthetic heart valve sewing cuffs [19] with silver were halted for safety reasons because of high silver levels in serum and excessive rates of perivalvular dehiscence, respectively.

CONCLUSION: PERSPECTIVE ON ASSESSING AND PREVENTING INFECTIONS ASSOCIATED WITH SURGICAL IMPLANTS

The serious medical consequences and soaring economic sequelae of infection associated with surgical implants underscore the importance of prevention. Considering the limitations on assessing the clinical efficacy of potentially preventive approaches and the nonstandardized application of antimicrobial strategies, it is only proper that we attempt to rectify this nonideal situation by addressing the following 4 issues.

Reduction in implant colonization versus implant-associated infection. In general, microbial colonization of the surgical implant is a prelude to implant-associated infection. However, as with central venous catheters, most cases of implant colonization do not result in clinical infection [13, 20]. As a corollary, a clinical trial may demonstrate that a particular antimicrobial strategy prevents implant colonization but may not be sufficiently powered to also demonstrate protection against clinical infection. Therefore, it would be prudent to carefully consider the clinical relevance of significantly reducing the rate of implant colonization, particularly if a statistically insignificant trend toward a lower rate of implant-associated infection is simultaneously demonstrated.

Pre- versus postmarketing clinical evaluation. In instances where financial and practical considerations hamper the ability to clinically assess the anti-infective efficacy of a newly developed antimicrobial carrier or antimicrobial-coated surgical implant before US Food and Drug Administration approval is obtained, it would be prudent to perform a postmarketing evaluation of clinical efficacy. However, the safety of such newly developed carriers or implants ought to be investigated before marketing by performing a small clinical trial directed at evaluating safety and/or by obtaining reasonable assurance of clinical safety from relevant in vitro and animal studies. The safety of such newly developed antimicrobial carriers or antimicrobial-coated surgical implants should be continually assessed after marketing.

Risk versus benefit of antimicrobial prophylaxis. Notwithstanding the fact that the clinical efficacy of antimicrobial prophylaxis against infections associated with surgical implants remains largely unconfirmed, we can potentially reap major medical and economic benefits by preventing such infections. The potential risks of antimicrobial prophylaxis include toxicity, allergic reaction, and antimicrobial resistance. Fortunately, the implementation of certain safety measures can help reduce the likelihood of developing such adverse events. For example, in the case of intravascular implants, it would be prudent to avoid local application of antimicrobial drugs that are considered unsafe for systemic administration (such as silver). Although placement of an antimicrobial carrier or an antimicrobial-

coated implant can theoretically elicit an allergic reaction to the administered antimicrobial, exclusion of patients with a history of allergic reaction to that particular antimicrobial should obviate the need for premature removal of these surgically placed items; this safety precaution has been successfully applied in cases of antimicrobial-coated catheter implantation. Historically, antimicrobial resistance has been linked mostly to inappropriate administration of systemic antibiotics. Much less information exists on the emergence of resistance to antimicrobial drugs (antibiotics or antiseptics) that are locally applied to prevent infections associated with surgical implants.

Systemic versus local antimicrobial prophylaxis. At the present time, we do not know how the clinical efficacy of systemic antimicrobial prophylaxis compares with that of local antimicrobial prophylaxis for the prevention of implant-associated infections, and it is unlikely that we will procure a clear answer anytime in the near future. Because systemic antimicrobial prophylaxis is additionally intended to prevent superficial wound infections, we cannot afford to rely solely on local administration of antimicrobial drugs to patients who will undergo surgical implantation. On the other hand, local antimicrobial approaches possess the advantage of providing higher local concentrations of antimicrobial drugs on and/or around the implant. Notwithstanding the potential practical and financial impediments, we need to better assess whether the combination of systemic and one form or another of local antimicrobial drugs truly provides more protection against implant-associated infection than does systemic antibiotic prophylaxis alone. Until then, the serious implications of implant-associated infections will simply disallow us from being able to recommend effectively that surgeons abolish certain existing nonstandardized preventive practices, much less to set new standards of infection prevention.

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