Molecular Pathogenesis of Surgical Infections

21st Fernström Symposium
Lund, June 1992

Edited by Torkel Wadström, Ian A. Holder and Göran Kronvall

Reprint

Gustav Fischer Verlag · Stuttgart · Jena · New York · 1994

Biomaterial-Associated Infections in Cardiothoracic and Vascular Surgery: Antimicrobial Bonding as an Interventional Strategy

Charles E. Edmiston, Jr., David Uyeno, G. Hossein Almassi, and Constantinos T. Frantzides

Surgical Microbiology Research Laboratory and Departments of General and Cardiothoracic Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin 53226 USA

Summary *Postsurgical infection following insertion of a prosthetic device is often associated with high morbidity. Infections occurring with surgical implant devices are recalcitrant to antibiotic therapy. Antibiotic bonding of surgical implants have demonstrated mixed results in preventing surface contamination and tissue infection, suggesting that the current bonding strategies are technique and drug dependent. Future acceptance and application of antibiotic bonding to bioprostheses hinges upon standardization of technique, reproducibility of biological activity, and awareness of potential tissue toxicity.*

Introduction

The overall risk of postsurgical infection has diminished over the last 40 years. This is due to a culmination of factors, the first being improvements in surgical technique, recognition of patient risk factors, appropriate surgical prophylaxis and the understanding of microbial pathogenesis in the surgical patient.[33] However, the widespread use of biomaterials in medicine has had a dramatic impact in potentiating the emergence of nosocomial infections which exhibits a recalcitrance to traditional antimicrobial therapy.[45]

In 1988, over 11 million Americans were the recipients of at least one implantable bioprosthetic device.[32] The rate of biomaterial-associated infection varies widely in medicine and surgery (Table 1). Infection rates for implantable biomaterials ranged from 1–3% for ocular implant to 100% for artificial organs such as the artificial heart.[18] The type of material used in the biomaterial and its spacial configuration often plays a major role in the overall risk of infection by: exhibiting a potential affinity for selective microbial pathogens, providing an environment in which microorganisms can

Table 1 *Incidence of Selective Biomaterial-Associated Infections.*

Intravascular line or catheters	5–25%
Orthopaedic prostheses	1–6%
Cardiothoracic implants	1–8%
Vascular prostheses	1–5%
Neurosurgical shunts	1–5%
Ocular prostheses	1–3%
Breast prostheses	1–4%
Artificial organs	100%

sequester within the interstices of the device or altering local host defense mechanisms through the disruption of host immune mechanisms.[14,29,46]

The use of bioprosthetic devices in cardiothoracic and vascular surgery has grown rapidly over the past 30 years. Intracardiac devices have been used since the late 1950's and include such appliances as mechanical valves, pacemaker generator and leads, and recently implantable cardioverter defibrillator (ICD) devices.[10] Large vessel graft replacement as a surgical procedure is almost 40 years old. A variety of synthetic textiles and polymers have been used during this period of time and at present velour knitted dacron and expanded polytetrafluoroethylene (ePTFE) are the most common replacement media in vascular surgery.[15] Host response to cardiothoracic and vascular implantable devices is influenced by size, composition and texture of the material. The individual structural and compositional characteristics of a bioprosthetic device often functions to enhance tissue reactivity to the device which has been shown by several investigators to influence the degree of postoperative risk of infection.[12,22,31]

Overt reactivity is often an undesirable characteristic if it prevents the full integration of the device within the tissues of the host. Furthermore, deleterious tissue interactions often alter the capacity of the host to respond to the presence of a potential microbial pathogen in the presence of the biomaterial. In addition, host responsiveness to infection is linked to age, metabolic competence and general well-being. At present, it is recognized that patients receiving an implantable bioprosthetic device are more likely to be in fair to poor health compared to age matched cohorts in the rest of the United States.[32] While overall infection rates are low in both cardiothoracic or vascular patients receiving an implantable prosthesis, infection when it occurs often has catastrophic consequences and contributes to the high incidence of morbidity associated with implant infection. Antibiotic bonding to inert prosthetic surfaces has been suggested as an effective strategy to minimize the risk of postoperative infection following prosthetic insertion. While several investigators have demonstrated the efficacy of antibiotic bonding to provide persistent drug levels over time, few studies have addressed the ability of bonded drug to prevent microbial adherence or colonization to prosthetic surfaces.

Microbial Epidemiology and Pathogenesis of Cardiothoracic and Vascular Prosthetic Infections

Biomaterial-associated infections are nosocomial infections in which virtually any organism can colonize the prosthetic surface. However, the staphylococci are the predominant pathogens recovered from infections of cardiothoracic and vascular devices.[1,2] The microbial etiology of any prosthetic device-related infection is almost always characterized as intrinsically endogenous. The staphylococci are a ubiquitous component of the skin and mucous membranes. Microbial contamination of a prosthetic device can occur via the skin, incisional margin, hair follicles, sweat glands or lymphatic structures at the time of surgery.[27] Contamination of a biomaterial surface through hematogenous seeding has been proposed as a possible mechanism of implant infection.[2] However, except for late occurring prosthetic valve (PVE) infections the evidence for this mechanism is mostly anecdotal and presently most infections of cardiothoracic or vascular implants are discerned as occurring at the time of insertion.

Clinically, the presentation of a cardiothoracic or vascular device infection can be characterized as either acute or late-onset. The coagulase negative staphylococci represent the major microorganisms recovered from PVE. Staphylococcus aureus and other organisms such as gram negative bacilli and nonenterocccal streptococci occur as minor pathogens in this process.[8] In addition, staphylococcal strains expressing multiple drug resistance are often recovered in blood cultures from patients with prosthetic valve endocarditis.[25] Cardiac pacemakers, along with implantable cardioverter defibrillators, (ICD) are highly complex devices with multiple components. Infections of the subcutaneous generator pocket are primarily acute infections which generally occur a few days to weeks postoperatively.[5,19] These infections are primarily caused by Staphylococcus aureus and are characterized by a purulent discharge from the generator pocket. Infection associated with the pacemaker leads most often occurs as a late onset complication (8 to 12 month postoperative) and Staphylococcus epidermidis accounts for almost all of these infections.[28] Rarely do we see gram negative bacteria or yeast recovered from these devices.

Over the last 10 years an increasing number of ICD devices have been inserted for the treatment of medically refractory malignant ventricular arrhythmias. While few clinical reviews have been published documenting the infection rate with these devices, the picture appears to be similar to that seen with permanent pacemakers. The patch material which is attached to the heart wall is composed of a silicone and titanium sheath (Figure 1a). This material, like other biomaterials, is susceptible to microbial colonization and the risk of infection with this device appears to be in the range of 1 to 7%.[1,35] Infections which present as a collection of purulent material in the generator pocket always necessitate removal of this device and a long course of systemic antibiotics. However, as appropriate prophylactic regimens are followed, we tend to

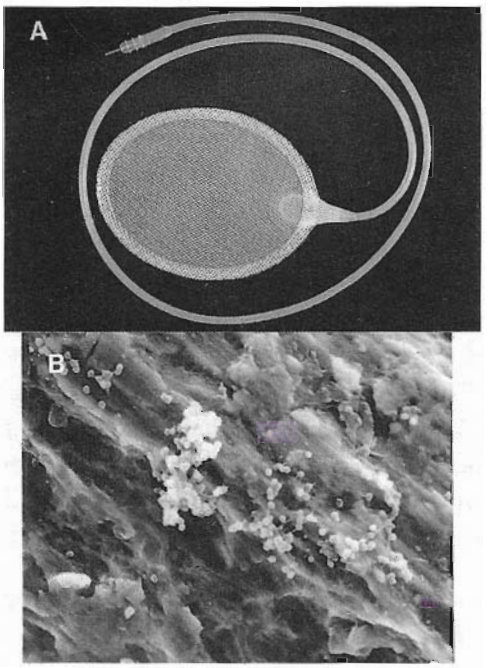

Figure 1. *A) Implantable cardioverter defibrillator (ICD) patch composed of silicone sheath and titanium mesh.*
B) ICD titanium demonstrating slime producing strain of Staphylococcus epidermidis sequestered on the pitted mesh surface (2150x).

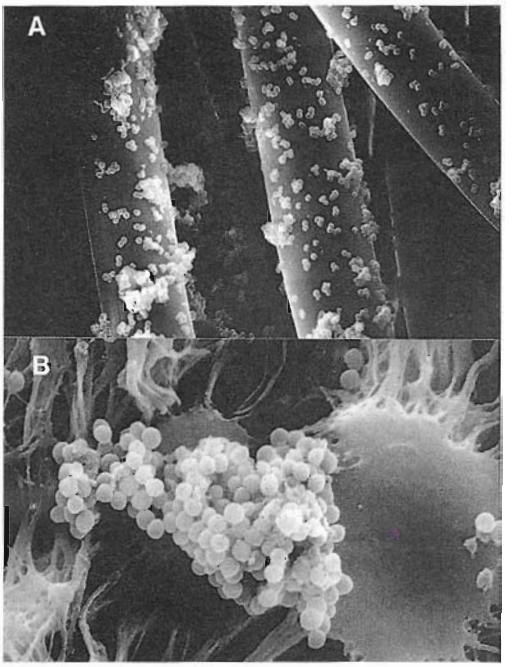

Figure 2. *A) Slime producing strain of Staphylococcus epidermidis colonizing fibers of velour knitted Dacron vascular graft (2000x).*
B) Adherence of non-slime producing strain of Staphylococcus epidermidis to surface of expanded polytetrafluoroethylene (ePTFE) graft (4800x).

find fewer and fewer of these acute infections and the emergence of more late-onset infections due to slime producing strains of Staphylococcus epidermidis. These infections often present without systemic manifestations of intrapericardial infection.[1] This is consistent with the presentation of other late-onset staphylococcal infections.[12,15] The recovery of this organism in culture is often difficult, which is due in part to inappropriate culture methodology. Slime producing strains of Staphyloccus epidermidis which colonize these devices, adhere tenaciously to the inert surface of the device and require vigorous vortexing or sonication to breakup the biofilm prior to culture.[37,41] Scanning electron microscopy of ICD patch surfaces has demonstrated that the slime producing staphylococci often sequester within the pitted surface of the titanium wire mesh (Figure 1b).

Infection of a prosthetic graft is a significant complication of peripheral arterial reconstruction and has an associated morbidity of 40–70% and a mortality of 30–50%.

While these infections like ICD infections are rare, they are surgical catastrophes when they do occur. These infections present as either acute or late-onset complications and the staphylococci are major clinical isolates in this disease process.[4] There is at present a decreasing frequency in the occurrence of acute onset disease which is due primarily to Staphylococcus aureus. Late-onset infections have been reported to occur from 12 to 70 months postoperatively. Studies in our laboratory have suggested that late-onset disease is biphasic, involving first the graft surface followed by a tissue phase which elicits a chronic inflammatory response ultimately leading to graft failure.[38,43] The graft phase of the infection is completely asymptomatic and it is during this period, which may continue for months or years, that the staphylococci multiply and persist within the fabric of the graft (Figures 2a,b). The outcome of this process, if not diagnosed in a timely fashion, results in graft erosion, sinus tract formation anastomotic dehiscence and finally, graft failure. A dilemma which was often faced in the diagnosis of late-onset infection was the failure to recover organisms from the explanted graft or perigraft exudate. The recognition that many of these grafts are colonized by slime producing staphylococci has led to the routine application of specimen sonication to disrupt the adherent biofilms and facilitate microbial recovery.

Prevention and Management of Cardiothoracic and Vascular Biomaterial-Associated Infection: Present Perspective

Efforts to prevent cardiothoracic and vascular device infections have focused on several fundamental strategies (Table 2). First, has been the recognition that biomaterial-associated infections are nosocomial infections acquired at the time of device insertion. Postsurgical monitoring of these devices for complications has often been difficult because of the long time interval between insertion and subsequent infection. However, in light of recent problems associated with other marketed biomaterials it is apparent that regulatory agencies such as the Food and Drug Administration (FDA) will take a more sentinel role in monitoring complications which occur following insertion of these devices. Surveillance is fundamental to our understanding of trends in the microbial etiology of device-related infections. A knowledge of the causal agent in these infections has allowed us to focus our preventive and treatment strategies against specific pathogen groups in an attempt to reduce the risk of postoperative infection.

Appropriate antimicrobial prophylaxis has been the foundation along with improvements in surgical technique in reducing the incidence of postsurgical infections.[23,33] Choice of agent, effective dosage, timing, route of delivery and duration are all important components in developing an appropriate prophylactic strategy.[6] The benefits derived from the appropriate use of antimicrobial prophylaxis in prosthetic

Table 2. *Prevention and Management of Cardiothoracic and Vascular Biomaterial-Associated Infections.*

Present Strategies	
Infection Control	
Knowledge of Potential Microbial Pathogen	
Appropriate Antibiotic Prophylaxis	
Minimal Tissue Damage and Exquisite Technique	
Removal of Infected Device – *in situ* replacement?	
Aggressive Debridement and Systemic Antibiotics	
Future Strategies	
Antibiotic Bonding to Prosthetic Surface	– Passive
	– Active
Antiseptic Surfaces	

device surgeries are numerous, not the least of which is the reduction in acute-onset septic episodes associated with Staphylococcus aureus infections.[11,21] Ironically however, a reduction in acute-onset disease may have been at the expense of an increased incidence of late-onset infection. Following the recognition of a device-related infection, often the surgeon has little alternative but to remove the implant and aggressively manage the infection with high dose antibiotics for an extended period of time. This usually follows extensive debridement of the implant site to remove any potentially infected tissues. The reluctance to manage most implant infections in situ is derived from the dismal record of therapeutic efficacy in attempting to clear the pathogen from the implant and surrounding tissues. Infections of prosthetic devices are almost always recalcitrant to antimicrobial therapy.[9,12] In the case of pacemaker and ICD infections, removal of the generator from the subcutaneous pocket is viewed as a necessary step in resolving the infection.[1,35] In some series, complete removal of the silicone/titanium leads and pulse generator followed by continuous irrigation of the subcutaneous pouch (10% povidone-iodine) and systemic antibiotics has proven effective. However, removal of the leads from the heart wall is a difficult process at best and is often made more difficult by the patient's advanced cardiac disease state.

Traditionally, the treatment of prosthetic graft infection has been high dose antibiotics and graft removal followed by revascularization of the effected limb. The morbidity and mortality associated with extra-anatomic revascularization is of such significant consequence that within the last 5 years an effort has been made to replace biofilm infected grafts in situ. Grafts which are infected with slime producing staphylococci (late-onset) are carefully removed along with the infected portions of the adjacent vessel walls.[3] The operative field is carefully debrided, irrigated and a new synthetic conduit sewn in place. Typically, an expanded polytetrafluoroethylene (ePTFE) graft is inserted as a replacement because of previous studies in our laboratory which demon-

strated a decreased staphylococcal adherence to this material compared to velour knitted dacron.[37] In addition, the patient receives a course of high dose antibiotics for several weeks (6 to 8) following surgery.

Treatment of an infected biomaterial device requires prompt, aggressive intervention. Failure to recognize a device-related infection in a timely fashion often leads to the development of other local or systemic sequelae which increases patient morbidity, complicating the overall management strategy.

Future Strategies to Prevent Device-Related Infections in Cardiothoracic and Vascular Surgery: Antibiotic Bonding

Because of the difficulty in eradicating bacteria from the site of an infected implant the surgeon is left in all too many cases with but a single option, removal of the prosthetic device. The essential purpose of antimicrobial prophylaxis is to provide adequate tissue levels at the time of surgical incision to preempt the development of a postoperative infection by bacteria contaminating the wound site. While this strategy has been successful at reducing the incidence of postsurgical contamination of the surgical wound, it is unlikely that the antimicrobial coverage extends to the surface of the inert prosthetic device. Furthermore, our laboratory and clinical experiences suggest that once colonization of the device occurs, therapeutic intervention has little chance of success.[17,44] The preventional strategy therefore should be directed at making the surface inhospitable for microbial colonization prior to device insertion.

Antibiotic incorporation into the biomaterial itself has been viewed as an early interventional approach for preventing bioprosthetic infection. Over twenty years ago, German investigators proposed the incorporation of antibiotic into orthopaedic bone cement at the time of total hip replacement.[7] Studies demonstrated that antibiotic incorporated into acrylic cement diffuses into the surrounding environment, often for days at levels which would in theory provide a high margin of therapeutic efficacy against implant infection. This procedure was rapidly embraced by orthopaedic surgeons in the United States and at present is considered a standard part of the orthopaedic practice. Most studies which have been undertaken to investigate the efficacy of this technique in the clinical practice have been poorly designed or flawed by sample bias. Furthermore, little evidence exists which validates the effect of antimicrobial incorporation on bacterial adherence and colonization to the bone cement surface. Studies conducted in our laboratory suggest that antibiotic incorporation into orthopaedic bone cement has a variable effect on microbial populations colonizing the surface of polymethylmethacrylate (PMM) bone cement (Figure 3). For example, tobramycin, while eliminating E coli from the surface of PMM has little effect on the three other reference strains, in spite of surface concentrations of tobramycin

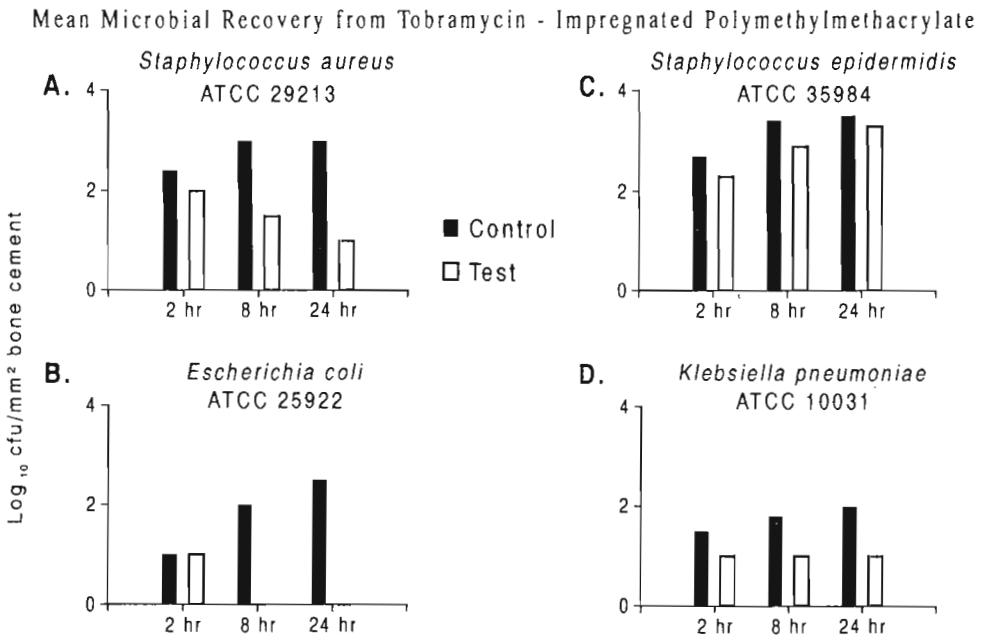

Figure 3. *Impact of tobramycin impregnated orthopaedic (polymethylmethacrylate) bone cement on microbial colonization. Figures 3A–D show mean microbial recovery from tests and controls for bacterial strains of different species.*

which were 4 to 5 times the minimal inhibitory concentration for the test strains.[40] Similar results have been found for gentamicin, cefazolin and selective quinolones. While high levels of antibiotic may be available in the environment of the prosthesis soon after surgery, it is likely that antibiotic incorporation into bone cement has little or no impact on selective gram-positive or gram-negative microbial adherence. In addition, it has been shown that PMM is antagonistic to host neutrophil function which may exacerbate the infectious process.[36] Since it is apparent from recent literature that appropriate antimicrobial prophylaxis has had a significant impact on reducing postoperative infections in orthopaedic surgery, the rationale for continued used of antibiotic impregnated acrylics is questionable.[34]

The alternative to incorporating antibiotic within the matrix of the biomaterial is the passive or active coating of the outer surface of the substrate with an antibacterial or antiseptic compound. Several reports have appeared in the literature over the past ten years which suggest the efficacy of antibiotic bonding of vascular grafts for preventing postsurgical infection.[16,20,26,39] A recent clinical study using antibiotic bonded intravascular catheters demonstrated a significant reduction in catheter related infections (14% control vs 2% bonded group) compared to a nonbonded control group.[24]

TABLE 3. *Antibiotic Bonding of Prosthetic Devices*

I. Prerequisites		
	Sensitivity and potency	
	Extended release into surrounding tissues	
	Stability in host	
	Non-allergenic - nonreactive	
	Agents of choice:	aminoglycosides (poor)
		fluoroquinolones
		rifampin
		glycopeptides
II. Techniques		
	Whole blood treatment	
	Platelet rich plasma treatment	
	Albumin treatment	
	Carrier moieties:	collagen
		benzalkonium chloride
		TDMAC
	Gelatin incorporation:	rifampin

There is at present a significant interest in antibiotic bonding of biomaterial surfaces from both an academic and commercial perspective. However, there are several separate but important issues which must be considered before the routine application of antibiotic bonded biomaterials is realized (Table 3). First is the issue of sensitivity and potency of the agent to be bonded to the inert surface. Because of our current understanding of biomaterial infections it is reasonable to predict with some degree of accuracy the pathogen most likely to colonize the surface of the device and select an antibiotic for bonding based upon that criteria. Drug availability at the surface of the device should be several times the MIC of the potential pathogen. However, local drug toxicity must be taken into consideration since overt tissue toxicity or drug hypersensitivity could be catastrophic for the patient. Duration of drug availability is another issue which at present is unresolved. It has been suggested that for percutaneous devices activity should be persistent over the life of the line or catheter, since these devices are at high risk for nosocomial infection and often experience daily manipulations or adjustment. Alternatively, the duration of antibiotic release from an implantable biomaterial should be of limited duration, possibly no more than 5 days post insertion. The rationale for this approach is vested in the fact that implant surgery is conducted under prophylactic antimicrobial coverage which in itself is protective against postsurgical infection. The use of an antibiotic bonded implant would be to provide an additional margin of protection against contamination of the device at the time of insertion. The choice of antimicrobial agents to be bonded to the device should

be dictated by a knowledge of the potential contaminating pathogen and the current resistance patterns observed within the institution. The aminoglycosides are a potentially beneficial class of compounds because of a broad spectrum of activity. However, these agents have proven to be unsatisfactory because of their poor bonding characteristics and the emergence of staphylococcal resistance within many institutions. The fluoroquinolones exhibit exceptional bonding characteristics; however, resistance has become a significant problem, especially with methicillin resistant strains of staphylococci. Rifampin is an agent which is currently being evaluated in antibiotic grafts in Europe. However, rifampin resistance has become a problem in some institutions and may possibly limit the useful application of this compound. The glycopeptides are a powerful class of agents which are highly active against the staphylococci. However, it is possible that vancomycin and the yet to be released teicoplanin are a much too valuable class of compounds to be considered for the routine use of antibiotic bonding to percutaneous or prosthetic devices. Finally, we should not overlook the potential application of incorporating antiseptic agents such as silver-sulfadiazine- chlorhexidine into biomaterials. A recent study has demonstrated that the use of antiseptic intravascular devices can reduce staphylococcal colonization and catheter related sepsis all without evidence of tissue toxicity.[30] It is likely that as this field expands additional therapeutic agents will be proposed as candidates for bonding to biomaterials.

A number of techniques have been used to actively or passively incorporate antibiotics onto the surface of a biomaterial (Table 3). For several years surgeons have attempted to coat implantable devices passively with antibiotics to provide an additional margin of protection against infection. Prior to insertion of velour knitted dacron graft some surgeons have precoated the device with whole blood or platelet rich plasma to which has been added a first generation cephalosporin such as cefazolin. Often cardiothoracic surgeons will simply rinse the implant in a basin containing an antibiotic solution prior to insertion. While no efficacy studies have ever been performed evaluating this rudimentary technique, it is likely the benefit is purely psychological (for the surgeon). Studies which have been published that document the sustained release of antibiotic from the biomaterial have all used a carrier agent to actively trap or bind the antimicrobial to the prosthetic surface. One such agent, a surfactant, tridodecylmethylammonium chloride (TDMAC), has been sucessfully used in bonding studies of antibiotic to vascular grafts.[16,20,26,39] TDMAC has been used in our laboratory to study the bonding of antimicrobial agents to several different biomaterials and its effect on in vitro activity.

High levels of cefazolin were observed following TDMAC bonding to Hickman catheters (Figure 4A). Drug activity was detected over a 120 hour period on both the Hickman surface and in the effluent surrounding the catheter segment (diluent changed daily). Studies to determine the effect of drug bonding on staphylococcal recovery from the catheter surface demonstrated a decrease in microbial recovery at 48 hours (Figure

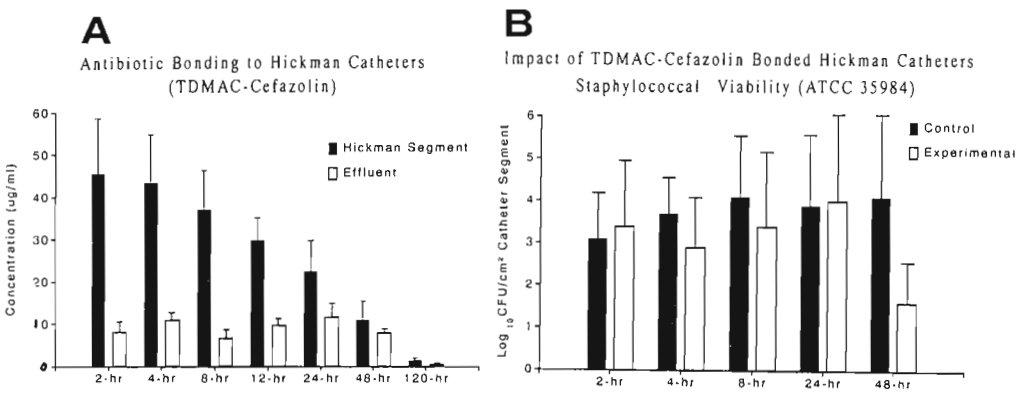

Figure 4. *A) Kinetics of Cefazolin bonded Hickman catheters. B) Mean staphylococcal recovered from Cefazolin bonded Hickman catheters.*

4B). While the findings of this study were not statistically significant (P=0.06), scanning electron microscopy (SEM) of catheter segments demonstrated decreased colonization of the catheter surface with time.

Studies of antibiotic bonding to automatic implantable cardioverter defibrillator (AICD) patch material demonstrated enhanced bonding of cefazolin when the TDMAC-silver was used in the bonding technique (Figure 5A). However, the levels of cefazolin present on the patch material after bonding was relatively low compared to the levels which were found in the Hickman catheter study. Furthermore, by 24 hours no cefazolin was detected in the TDMAC group. The TDMAC-silver bonding technique effectively demonstrated persistent levels of cefazolin over the 5 day test period. The effect of drug bonding on staphylococcal viability over 48 hours was inconclusive with the exception of the silver-drug bonded group (Figure 5B). The silver-drug group demonstrated a 3 to 4 fold-log drop in staphylococcal recovery from the AICD patch material. When a quinolone was bonded to the silicone/titanium patch material, a two-fold increase was observed in drug activity in the silver and TDMAC-silver drug groups. A corresponding 4 to 5 log decrease ($P<0.05$) was observed in staphylococcal colonization of the AICD patch material when the quinolone ciprofloxacin was used in bonding studies.[42]

Finally, studies of antibiotic bonding to vascular grafts have been performed in our laboratory utilizing several classes of agents. High levels of cefazolin have been achieved in velour knitted dacron grafts using a variety of bonding methodologies

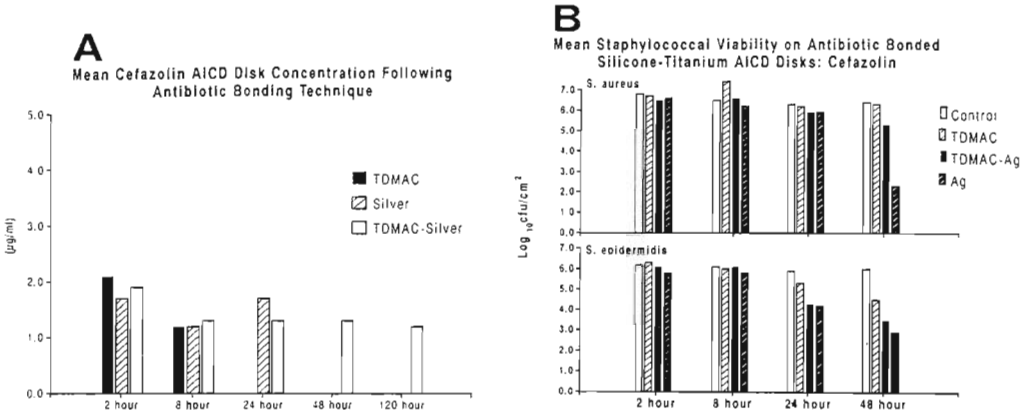

Figure 5. *A) Kinetics of Cefazolin bonded automatic implantable cardioverter defibrillator (AICD) patch material. B) Mean staphylococcal recovery from Cefazolin bonded AICD patch material.*

(Figure 6A). Drug levels released from the surface of the grafts were consistently above expected MIC values for most staphylococcal contaminants (excluding methicillin resistant strains). Studies performed to assess the effect of bonding on staphylococcal viability demonstrated a statistically significant decrease ($P<0.05$) in viability at 120 hours in all three test groups (Figure 6B). Furthermore, no staphylococci were detected on the surface of the TDMAC-silver bonded group at 120 hours by culture or SEM. When the glycopeptide, teicoplanin was bonded to Dacron grafts, extremely high levels of the drug were detected by biological assay (Figure 7A). The levels observed at 4 hours were 1500 to 4000 times the MIC of the test staphylococcal strains. At 5 days the levels were in the range of 10 to 20 times the MIC. Corresponding studies to determine the effect of these levels on staphylococcal colonization revealed a significant decrease ($P<0.05$) in viable staphylococcal recovery at 24 hours. By 48 hours no organisms could be detected on the graft surface by sonication culture or SEM (Figure 7B). The standard protocols used in antibiotic bonding studies suggest that 50 mg/ml of drug is an appropriate concentration for biomaterial bonding. However, as the previous studies suggest, final drug levels vary widely based upon the composition of the specific biomaterial and the method used to bond the drug to that device.

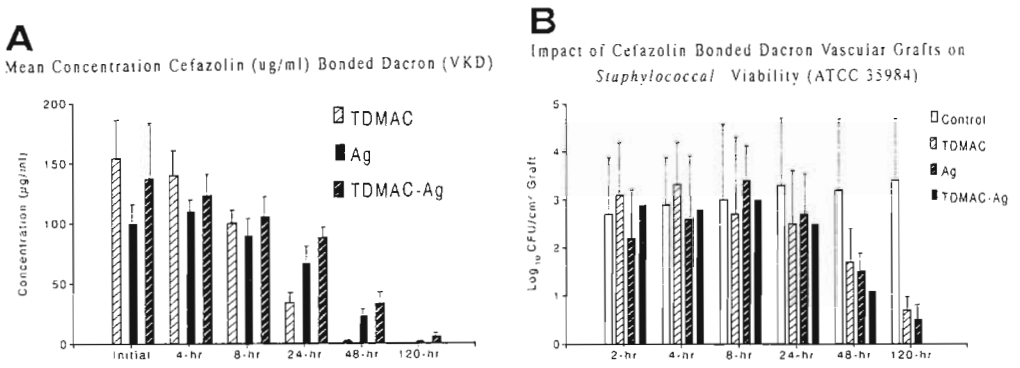

Figure 6. *A) Kinetics of Cefazolin bonded velour knitted Dacron (VKD) vascular graft material. B) Mean staphylococcal recovery from Cefazolin bonded VKD vascular graft material.*

Conclusions

Bonding of antibiotics to an inert surface is highly drug, biomaterial, and possibly investigator dependent. Furthermore, several reports have suggested that in specific instances antibiotic (quinolone) bonding to a biomaterial surface may demonstrate an anti-adhesive effect. In our laboratory we have never witnessed this phenomena on a biologically inert surface. It is unlikely given the dynamics of microbial adherence that an antibiotic alone on the surface of a vascular graft or ICD patch will interrupt the adherence of a contaminating staphylococci at the time of insertion. It may however, prevent colonization and/or persistence of that organism on the biomaterial and in the tissues surrounding the implant.

It is obvious from the orthopaedic cement studies that adequate drug levels in the polymethylmethacrylate did not ensure eradication of organisms from the surface of the resin. Numerous in vitro studies have demonstrated a microbial recalcitrance to antimicrobial agents in the presence of various biomaterials used as surgical implants.[9,13,17,44] However, this should not be simply interpreted as acquired resistance mediated by the presence of the biomaterial. On the contrary, failure to eradicate a bacteria from the surface of an antibiotic bonded biomaterial may be merely the expression of an organism existing in a reduced metabolic state. Our assumptions concerning microbial killing are based almost solely on in vitro tube studies and often fail to take into consideration the environment within and around the biomaterial

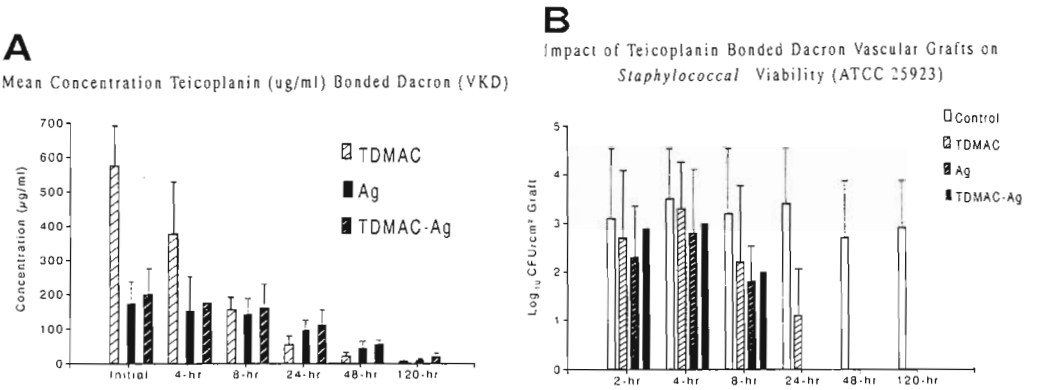

Figure 7. *A) Kinetics of Teicoplanin bonded velour knitted Dacron (VKD) vascular graft material. B) Mean staphylococcal recovery from Teicoplanin bonded VKD vascular graft material.*

implant. At present, the technique of antibiotic bonding is highly labor intensive and no published data is available on the reproducibility of the various bonding strategies. Before there is a commercial effort to market antibiotic bonded devices, tight quality control parameters must be established for both drugs and the biomaterials to which they will be bonded. In addition, there is the possibility that widespread use of antibiotic bonded biomaterials in the practice of medicine and surgery will exacerbate the global problem of nosocomial resistance. While it is difficult to adequately predict the potential impact this technique will have on the emergence of resistant microbial strains, it is never-the-less reasonable to assume that intensive use of antibiotic bonded devices (lines, catheters, prosthetic implants) will place additional antimicrobial pressures upon our endogenous microbial populations.

Strategies to prevent and manage device-related infections are fundamentally developed through carefully designed and executed laboratory experiments followed by clinical trials. It is an educated guess that clinical application will occur within 5 years in the United States and possibly earlier in Europe. Whether or not antibiotic bonded biomaterials have a major impact in reducing the risk of nosocomial infection in the critically ill or implant patient remains to be seen.

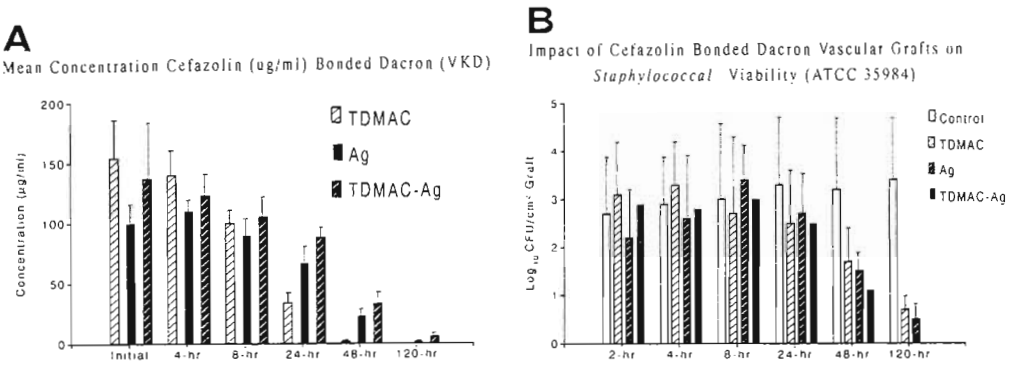

Figure 6. *A) Kinetics of Cefazolin bonded velour knitted Dacron (VKD) vascular graft material. B) Mean staphylococcal recovery from Cefazolin bonded VKD vascular graft material.*

Conclusions

Bonding of antibiotics to an inert surface is highly drug, biomaterial, and possibly investigator dependent. Furthermore, several reports have suggested that in specific instances antibiotic (quinolone) bonding to a biomaterial surface may demonstrate an anti-adhesive effect. In our laboratory we have never witnessed this phenomena on a biologically inert surface. It is unlikely given the dynamics of microbial adherence that an antibiotic alone on the surface of a vascular graft or ICD patch will interrupt the adherence of a contaminating staphylococci at the time of insertion. It may however, prevent colonization and/or persistence of that organism on the biomaterial and in the tissues surrounding the implant.

It is obvious from the orthopaedic cement studies that adequate drug levels in the polymethylmethacrylate did not ensure eradication of organisms from the surface of the resin. Numerous in vitro studies have demonstrated a microbial recalcitrance to antimicrobial agents in the presence of various biomaterials used as surgical implants.[9,13,17,44] However, this should not be simply interpreted as acquired resistance mediated by the presence of the biomaterial. On the contrary, failure to eradicate a bacteria from the surface of an antibiotic bonded biomaterial may be merely the expression of an organism existing in a reduced metabolic state. Our assumptions concerning microbial killing are based almost solely on in vitro tube studies and often fail to take into consideration the environment within and around the biomaterial

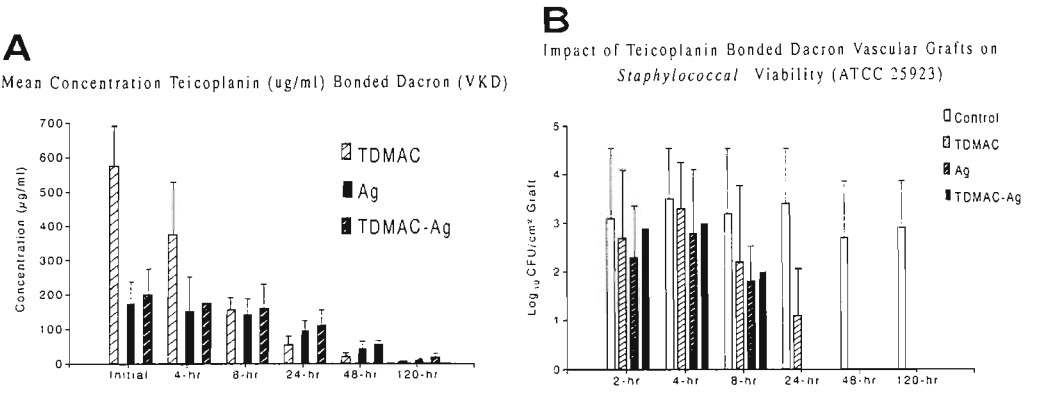

Figure 7. *A) Kinetics of Teicoplanin bonded velour knitted Dacron (VKD) vascular graft material. B) Mean staphylococcal recovery from Teicoplanin bonded VKD vascular graft material.*

implant. At present, the technique of antibiotic bonding is highly labor intensive and no published data is available on the reproducibility of the various bonding strategies. Before there is a commercial effort to market antibiotic bonded devices, tight quality control parameters must be established for both drugs and the biomaterials to which they will be bonded. In addition, there is the possibility that widespread use of antibiotic bonded biomaterials in the practice of medicine and surgery will exacerbate the global problem of nosocomial resistance. While it is difficult to adequately predict the potential impact this technique will have on the emergence of resistant microbial strains, it is never-the-less reasonable to assume that intensive use of antibiotic bonded devices (lines, catheters, prosthetic implants) will place additional antimicrobial pressures upon our endogenous microbial populations.

Strategies to prevent and manage device-related infections are fundamentally developed through carefully designed and executed laboratory experiments followed by clinical trials. It is an educated guess that clinical application will occur within 5 years in the United States and possibly earlier in Europe. Whether or not antibiotic bonded biomaterials have a major impact in reducing the risk of nosocomial infection in the critically ill or implant patient remains to be seen.

References

1. Almassi GH, Olinger GN, Troup PJ, Chapman PD, Goodman LR. Delayed infection automatic implantable cardioverter-defibrillator. J Thorac Cardiovasc Surg 95:908–911, 1988.
2. Bandyk DF. Vascular graft infections: Epidemiology, bacteriology, and pathogenesis. In Bernhard VM, Towne JB, (Eds), Complications in Vascular Surgery, 2nd edition. Grune & Stratton Inc, Orlando, Fl. pp. 471–485, 1985.
3. Bandyk DF, Bergamini TM, Kinney EV, Seabrook JB, Towne, JB. In situ replacement of vascular prostheses infected by bacterial biofilms. J Vasc Surg 13:575–583, 1991.
4. Bandyk DF, Berni GA, Thiele BL, Towne JB. Aorotofemoral graft infection due to Staphylococcus epidermidis. Arch Surg 119:102–108, 1984.
5. Beeler BA. Infections of permanent transvenous and epicardial pacemakers in adults. Heart Lung 11:152–157, 1982.
6. Bergamini T, Polk HC. Pharmacodynamics of antibiotic penetration of tissue and surgical prophylaxis. Surg Gynecol Obstet 168:283–294, 1989.
7. Buchholz HW, Gartmann HD. Infektions prophylaxe und operative behandlung der schleichenden tiefen infektion bei der totalen endoprosthese. Chirurg 43:446–458, 1972.
8. Calderwood SB, Swinski LA, Waternaux CM. Risk factor for the development of prosthetic valve endocarditis. Circulation 72:31–38, 1985.
9. Chuard C, Lucet JC, Rohner P, Hermann M, Aukenthaler R, Waldvogel FA, Lew DP. Resistance of Staphylococcus aureus recovered from infected foreign body in vivo to killing by antimicrobials. J Infect Dis 163:1369–1373, 1991.
10. Dickinson GM, Bisno AL. Infections associated with indwelling devices: Concepts of pathogenesis; infections associated with intravascular devices. Antimicrob Agents Chemother 33:597–601, 1989.
11. DiPiro JT, Bowden TA, Hooks VH. The prophylactic use of cephalosporins for surgery. JAMA 263:1839–1144, 1985.
12. Dougherty SH, Simmons RL. Infections in bionic man: The pathobiology of infection in prosthetic devices. Part I. Curr Prob Surg 19:221–268, 1982.
13. Dunne WM. Effect of subinhibitory concentrations of vancomycin or cefamandole on biofilm production by coagulase negative staphylococci. Antimicrob Agents Chemother 34:390–393, 1990.
14. Edmiston CE, Schmitt DD, Seabrook GR. Coagulase–negative staphylococcal infections in vascular surgery: Epidemiology and pathogenesis. Infect Control Hosp Epidemiol 10:111–117, 1989.
15. Edmiston CE, Schmitt DD, Seabrook GR. Etiology and pathogenesis of late–onset vascular graft infections. In: Wadstron T, Eliasson I, Holder I, Ljungh A, (Eds), Pathogenesis of Wound and Biomaterial–Associated Infections. Berlin, Springer-Verlag pp. 465–478, 1990.
16. Greco RS, Harvey RA. The role of antibiotic bonding in the prevention of vascular prosthetic infection. Ann Surg 195:168–173, 1982.
17. Gristina AG, Jennings RA, Naylor PT, Myrvik QN, Webb LX. Comparative in vitro antibiotic resistance of surface colonizing coagulase-negative staphylococci. Antimicro Agents Chemother 33:813–816, 1989.
18. Gristina AG, Naylor PT, Myrvik QN. Biomaterial-centered infections: microbial adhesion versus tissue integration. In: Wadstron T, Eliasson I, Holder I, Ljungh A, (Eds), Pathogenesis of Wound and Biomaterial-Associated Infections. Berlin, Springer-Verlag pp. 193–216, 1990.
19. Harjula A, Jarvinem A, Virtanen KS. Pacemaker infections: Treatment with total or partial pacemaker system removal. Thorac Cardiovasc Surg 33:218–224, 1985.
20. Harvey RA, Alcid CV, Greco RS. Antibiotic bonding to polytetrafluoroethylene with tridodecylmethylammonium chloride. Surgery 92:504–509, 1982.

21. Hopkins CC. Antibiotic prophylaxis in clean surgery: peripehral vascular surgery, noncardiovascular thoracic surgery, herniorrhaphy, and mastectomy, Rev Infect Dis 13 (suppl 10):S869–S882, 1991.

22. James GM, MacLeod CJ. Induction of staphylococcal infection in mice with small inocula introduced on sutures. Br J Exp Pathol 42:266–274, 1961.

23. Kaiser AB. Antimicrobial prophylaxis in surgery. N Eng J Med 315:1129–1138, 1986.

24. Kamal GD, Pfaller MA, Rempe LE, Jebson PJR. Reduced intravascular catheter infection by antibiotic bonding. JAMA 265:2364–2368, 1991.

25. Karchmer AW, Archer GL, Dismukes WE.: Staphylococcus epidermidis causing prosthetic valve endocarditis: Microbiologic and clinical observations as guides to therapy. Ann Intern Med 98:447–456, 1983.

26. Kinney EV, Bandyk DF, Seabrook GR, Kelly HM, Towne JB. Antibiotic-bonded PTFE vascular grafts: the effect of silver antibiotic on bioactivity following implantation. J Surg Res 50:430–435, 1991.

27. Levy MF, Schmitt DD, Edmiston CE, Bandyk DF, Krepel CJ, Seabrook GB, Towne JB. Sequential analysis of staphylococcal colonization of surfaces of patients undergoing vascular surgery. J Clin Microbiol 28:664–669, 1990.

28. Lewis AB, Hayes DL, Holmes DR. Update on infections involving permanent pacemakers: Characterization and management. J Thorac Cardiovasc Surg 89:758–767, 1985.

29. Lugwicka A, Jansen B, Wadstrom T, Pulverer G. Attachment of staphylococci to various synthetic polymers. Zentralbl Bakteriol Mikrobiol Hyg A 256:479–489, 1984.

30. Maki DG, Wheeler SJ, Stolz SM, Mermel LA. Clinical trial of a novel antiseptic central venous catheter. 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, Pg. 176, October 1, 1991.

31. McGeehan D, Hunt D, Chaudhuri A. An experimental study of the relationship between synergistic wound sepsis and suture material. Br J Surg 67:636–642, 1980.

32. Moss AJ, Hamburger S, Moore RM, Jeng LL. The use of selected medical implants in the United States, 1988. Advance data from vital and health statistics; no. 191. Hyattsville, MD: National Center for Health Statistics. 1990.

33. Nichols RL. Surgical Wound Infection. In: Martone WJ, Garner JS, (Eds), Proceedings of the third decennial international conference on nosocomial infections. Am J Med 91:54S–64S, 1991.

34. Norden CW. Antibiotic prophylaxis in orthopaedic surgery. Rev Infect Dis 13(suppl 10):S842–S853, 1991.

35. Olinger GN, Chapman PD, Troup PJ, Almassi GH. Stratified application of the automatic implantable cardioverter defibrillator. J Thorac Cardiovasc Surg 96:141–149, 1988.

36. Panush RS, Petty RW. Inhibition of human lymphocyte response by methylmethacrylate. Clin Ortho Rel Res 134:356–364, 1978.

37. Schmitt DD, Bandyk DF, Pequet AJ, Towne, JB. Bacterial adherence to vascular prostheses: A determinant of graft infectivity. J Vasc Surg 3:732–740, 1986.

38. Seabrook GR, Schmitt DD, Bandyk DF, Edmiston CE, Krepel CJ, Towne JB. Anastomotic femoral pseudoaneurysm: a prospective investigation of occult infection as an etiologic factor. J Vasc Surg 11:624–628, 1990.

39. Shah PM, Modak S, Fox CL, Babu SC, Sampath L, Clauss RH, Stahl WM. PTFE graft treated with silver-norfloxacin: drug retention and resistance to bacterial challenge. J Surg Res 42:298–303, 1987.

40. Siverhus DJ, Edmiston CE, Steihl JB, Goheen MP. Microbial adherence and colonization of antibiotic impregnated methylmethacrylate bone cement. 37th Annual Meeting of the Orthopaedic Research Society. Anaheim, CA., pg. 6, April 19, 1991.

41. Tollefson DF, Bandyk DF, Kaebnick HW, Seabrook GB, Towne, JB. Surface biofilm disruption: Enhanced recovery of microorganisms from vascular prostheses. Arch Surg 122:38–43, 1987.

42. Uyeno D, Edmiston CE, Almassi H, Krepel C, Gohr C, Olinger G. Influence of antibiotic bonding to cardiothoracic implantable

biomaterial on staphylococcal colonization. 5th Annual Meeting of the Surgical Infection Society - Europe. Santiago de Compestela, Spain, pg. 32, June 8, 1992.

43. **Vetsch R, Bandyk DF, Schmitt DD, Bergamini TM, Storey JD, Towne JB.** Anastomotic tensile strength following in situ replacement of an infected abdominal aortic graft. Arch Surg 124:425–428, 1989.

44. **Wilson C, Seabrook GB, Edmiston CE, Krepel, C.** In vitro antibiotic resistance of slime producing coagulase-negative staphylococci growing on knitted Dacron vascular grafts. 91st General Meeting of the American Society for Microbiology, Dallas, TX., pg. 18, May 20, 1991.

45. **Young EJ, Sugarman B.** Infections in prosthetic devices. Surg Clin North Amer 68:187-198, 1988.

46. **Zimmerli W, Lew PD, Waldvogel FA.** Pathogenesis of foreign body infection; Evidence for a local granulocytic defect. J Clin Invest 73:1191–1199, 1984.