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Strategies for Prophylaxis against Prosthetic Valve Endocarditis: A Review Article

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Prosthetic valve endocarditis (PVE) is an important cause of the morbidity and mortality associated with heart valve replacement surgery. Once established, it carries a mortality rate that may be as high as 70%. The only treatment for established PVE is rigorous intravenous antimicrobial therapy, although this has extremely limited success. The majority of cases require surgical removal and replacement of the infected prosthesis. At present, the only means of preventing PVE are scrupulous asepsis and prophylactic perioperative antibiotic therapy. If another strategy could be developed that is effective and safe, the incidence of this disastrous complication of valve replacement would be reduced. Such strategies have been extensively investigated from a variety of different perspectives for several years. The understanding of biofilms appears to be pivotal to the development of a successful approach. The historic background to the prevention of PVE, and the current state of research into this area are discussed.

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Prosthetic valve endocarditis (PVE) is an important cause of the morbidity and mortality associated with heart valve replacement surgery, the current mortality rate being quoted as high as 70% (1-6). It has presented as a serious complication since valve replacements were first performed, and many cases have been reported in the literature, dating as far back as 1961 (7). Once established, PVE presents a number of difficult management problems, and in many cases, requires reoperation for removal and replacement of the infected prosthesis. The reoperation may need to be performed as an emergency in severely compromised patients, and the mortality rate of such procedures is high. The initial treatment for PVE is administration of systemic antibiotics, initially given intravenously in high doses. Unfortunately, even with antibiotic therapy, reoperation is often required. Hence, attention has more recently turned to prophylaxis against the occurrence of PVE, and a number of different approaches have been tried.

It is becoming increasingly clear that the root of the problem is the establishment of resilient biofilm bacteria around the prosthesis, rather than the free-circulating organisms that are traditionally targeted. With this in mind, the focus has changed, and much research is now directed at this specific approach. If a safe and efficient method of preventing the onset of infection in prosthetic heart valves could be found, it would have major implications for cardiac surgery.

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Biofilm etiology of endocarditis

Biofilms contain populations of bacteria that have attached themselves to surfaces, and have surrounded themselves with very large amounts of exopolysaccharide slime (8-10). These sessile communities are very firmly adherent to the colonized surfaces, and their component cells are extensively modified as they adhere and adapt to this stationary mode of growth (11). In high flow systems, such as the heart, biofilms develop a very high tensile strength, as they do in dental plaques and in high-pressure pipelines (12,13). Bacterial cells within biofilms have been shown to be resistant to 500-1,500 times the concentrations of sterilants and antibiotics that will readily kill floating (planktonic) cells of the same species (14,15). Direct observations of the biofilm 'vegetations' formed on native heart valves by cells of the viridans group of streptococci (16) show that the bacterial cells are embedded in a complex matrix of their own exopolysaccharide slime, mixed blood polymers and the debris of unsuccessful phagocytosis. Biofilms on mechanical and porcine

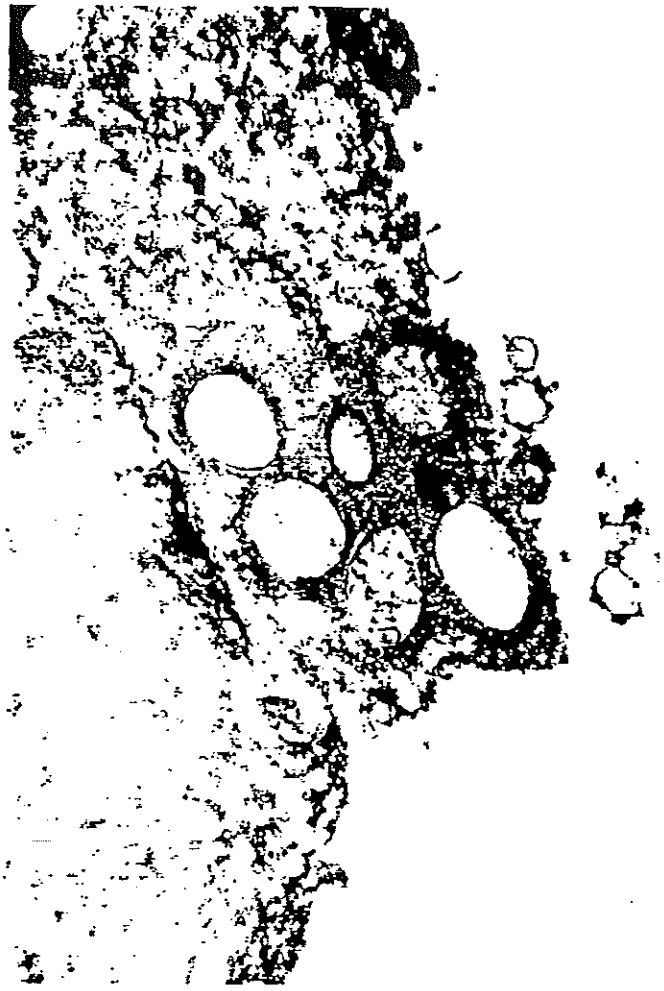

Figure 1: Matrix-enclosed microcolony of viridans group streptococci on the aortic valve (rabbit model).

valves contain more bacterial cells by volume, but host materials still make up a significant portion of these macroscopic vegetations. Figure 1 shows a matrix-enclosed microcolony of viridans group streptococci in a vegetation on the aortic valve in experimental endocarditis in the rabbit model. This image can, perhaps, guide the treatment of native valve infective endocarditis (NVE) and PVE, because the causative bacteria are actually very firmly attached to the native and prosthetic valves in macroscopic biofilms composed of their own exopolysaccharides and of host material.

Because of the very high rate of blood flow past valves that are affected by endocarditis, it is unlikely that any of the bacteria causing this disease are present in the planktonic phenotype that is specifically targeted by all currently available antibiotics (8). The biofilm phenotype of these bacteria, which is profoundly different from that of the floating cells of the same species, is extremely resistant to these antibiotics (14), and it is unlikely that antimicrobial therapy will succeed. Some success is seen in the treatment of subacute bacterial endocarditis (SBE), because the bacterial biofilms grow on surfaces that are fully in contact with high circulating levels of antibiotics. However, PVE is especially resistant because some of the causative biofilms are 'hidden' in cryptic areas and within the sewing ring, and simply are not exposed to concentrations of antibiotics that can be effective against the naturally resistant sessile bacteria. It is especially sobering to note here that, if pre-formed bacterial biofilms are introduced into the body on the surfaces of medical devices, their natural resistance to host defense mechanisms (antibodies, phagocytosis) will allow them to cause overt infections in virtually every case. This was demonstrated by Ward et al. who placed biofilm-colonized plastic discs into the peritoneums of rabbits that had been immunized against the organisms in the biofilms, and showed that all of the animals developed device-related infections (17).

PVE and NVE probably constitute the most clear-cut examples of biofilm infections (in the presence and absence of a medical device, respectively), because some of the surfaces colonized by these bacteria are obviously bathed by blood at very high shear rates. For this reason it is salutary to consider some of the factors that have been examined in connection with biofilm formation in engineered systems with similarly high shear rates (Reynolds numbers >2,000). Bacteria form biofilms very readily in high-shear systems (18) because of impingement in the turbulent flow zone closest to the surface, and surface irregularities are pivotal because they affect turbulent flow. Bacterial biofilms shed planktonic cells by a natural detachment process, and they also shed biofilm fragments composed of matrix-enclosed cells in the biofilm phenotype when they are stressed or manipulated. Biofilm fragments detached from endocardial surfaces travel, in the pulmonary artery or in the aorta, until they lodge in a capillary bed. The biofilm literature, in both microbiology and engineering, can perhaps contribute to clinical decisions in the management of patients who are unfortunate enough to have acquired bacterial biofilms on artificial surfaces, in high-shear environments of crucial importance to their survival.

The pathogenesis of prosthetic valve endocarditis

A large number of organisms have been identified as directly causative of PVE, and these have been extensively outlined in previous reviews (6). The most common are the same ones that cause NVE on natural valves. If PVE is traditionally divided into the early (within 60 days of surgery) and late (>60 days following surgery) types, there is a predominance of staphylococcal infection in early PVE, most likely due to poor

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aseptic technique and surgical contamination (19,20). *Staphylococcus epidermidis* is a much more common cause of PVE than *Staphylococcus aureus*, except in intravenous drug abusers (21). Transient bacteremia is the main cause of late PVE, frequently by the viridans forms of streptococcus, but a whole spectrum of Gram-positive, Gram-negative and fungal organisms may be responsible. In some cases, less virulent organisms, such as coagulase-negative staphylococci, may be inoculated perioperatively, but do not cause clinical disease until months or even years after valve implantation. Some other organisms, such as atypical mycobacteria, almost exclusively cause endocarditis in the presence of cardiac prostheses (22,23). The increase in the frequency of fungal endocarditis is attributable to prosthetic valvular implants, intravenous catheters, and prolonged antibacterial therapy (24).

The incidence of endocarditis following heart valve replacement is variably quoted, but is approximately 0.4% per year (2,6,21,25-27). Although the incidence of PVE is decreasing, the absolute number of cases is increasing, probably reflecting the larger number and more complex nature of procedures now being performed. PVE constitutes 15 to 20% of all cases of endocarditis (21). It has been suggested that PVE is more common in aortic valve replacements (AVR) than mitral valve replacements (MVR) (19,28). However, a large meta-analysis performed recently has demonstrated that this is not so, and there is in fact no difference in the incidence of PVE between the two (6). The incidence of PVE in xenografts, or bioprostheses, is similar to that of mechanical prostheses (29,30). The main pathologic finding in PVE is paravalvular abscess, which leads to dehiscence, paravalvular leaks, and regurgitation. Necropsy studies have shown that in most cases of infection of mechanical prostheses, the infection initially involves the sewing ring, then spreads to the annulus and surrounding tissues, and goes on to form an abscess (6,31).

Infection in bioprostheses may spread to the leaflets, tearing or perforating them, but ring abscesses are less common (32). Infection is, however, more likely to be localized to the cusps, resulting in perforation and their progressive destruction. Homograft endocarditis presents in a rather similar fashion, though with some differences. The infection is initiated in the leaflets and spreads to destroy the graft quite rapidly, causing symptoms of gross regurgitation at an early stage (33).

Several risk factors for the development of PVE have been identified. Calderwood et al. reported an actuarial risk of 3.1% at 12 months and 5.7% at 60 months after surgery (34). These figures have been revised recently to give risks of 0.4-0.8% at 12 months, and approximately 2% at 60 months, perhaps reflecting improved standards and knowledge over the past ten years (6). Although most investigators differ slightly in their findings, factors that appear to be important in the development of PVE include native endocarditis, male gender, long cardiopulmonary bypass time, black race, and mechanical prosthesis (3,35). Although the risk of infection of mechanical heart valves surpasses that of bioprostheses during the first three months following surgery, the rates of infection for the two converge later and become similar at five years.

Prognosis is dependent upon a number of factors, not all related to the valve infection. By combining all cases, the mortality of PVE is probably between 50 and 70% (1,2,6). Studies on the natural history of PVE indicate that early-onset infection carries a much higher morbidity and mortality than late-onset infection (36). Although it has been reported that the prognosis for late-onset PVE involving an already endothelialized valve surface is similar to that of native valve endocarditis, there are studies that dispute this belief (20).

Not surprisingly, sources of early postoperative infection include surgical wounds, urinary catheters, blood contamination by oxygenator, bypass circuit and pump prime, and human contamination from skin and instruments. While on the ward postoperatively, further sources are the sternotomy wound, infected pleural effusions, chest infections, and indwelling catheters, cannulas and drains. Common sources of late infection are urinary tract and airway infections, staphylococcal skin lesions and dental procedures.

Clinical presentation generally includes a pyrexia of varying degrees, and is found in up to 97% of cases (21,37). A new murmur usually represents a paravalvular leak, and a number of signs and symptoms may be present, as for native NVE, but the diagnosis is usually much easier in PVE due to the history of valve replacement surgery. All the documented complications of NVE, such as heart failure and embolic phenomena, may also occur with PVE, but there are some that are specific to PVE, such as progressive obstruction in the caged-ball type of valve. Once diagnosed, PVE must be treated promptly in all cases.

At present, preventive practice consists of scrupulous aseptic technique and systemic antibiotic prophylaxis. Although new technology will never alleviate the need for this existing practice, it is hopeful that a combined approach will greatly reduce the incidence of this life-threatening condition.

Current practice

Manufacturing

Manufacturing of valves is a complex and multistage process, and it is crucial that asepsis is assured throughout. Although some processes may vary slightly between different manufacturers, in general all com-

nents are initially depyrogenated before assembly. Depyrogenation usually utilizes chemical or thermal methods depending on the nature of the material. Mechanical prostheses are then steam or ethylene oxide sterilized, to assure sterile packaging. The most common method of sterilization for tissue valves is glutaraldehyde fixation combined with isopropyl alcohol and formaldehyde treatment. All commercially produced valves are manufactured under aseptic conditions with microbiological control and surveillance to ensure sterility, the full details of which are too lengthy to be reported here.

Aseptic techniques

The valve is probably at most risk of becoming infected during the time between opening the sterile valve container and closure of the chest post implantation. Aseptic techniques in the operating room are emphasized, but do not eliminate the potential for inoculating infective agents. The majority of surgeons currently use water-impermeable drapes, and a new, clean set of sterile towels to cover the wound edges and retractors while the valve is being implanted. Inadequate scrubbing and glove perforations are two of the more common risk factors, and fortunately can be prevented. Attention to hemostasis on closure to avoid hematoma formation in the wound must not be underestimated. If the wound becomes infected, the risks of PVE increase enormously, as dehiscing sternal infections and mediastinitis are frequently catastrophic. A number of topical approaches have been proposed to maintain as sterile an environment as possible. Many surgeons 'paint' the skin and subcutaneous tissues with aqueous iodine solution immediately prior to closure, and others use a warm saline and antibiotic 'washout' of the mediastinal cavity. Antibiotic powders can be used and sprinkled over the operation site in the mediastinum, particularly in high-risk patients.

Postoperatively, scrupulous care must be taken to avoid potential portals of infection, and intravenous catheters, if required, should be regularly changed. It should, however, be noted that extensive investigations have failed to identify any elements of intraoperative technique or postoperative care in need of improvement or modification (38).

Systemic antibiotics

Prophylactic antibiotic therapy is administered to all patients undergoing valve replacement surgery, usually commencing at induction of anesthesia, and continued for 24 hours. It usually takes the form of bolus intravenous doses of a broad-spectrum agent. Cephalosporins with high activity against Gram-positive bacteria are probably the most widely used agents, although vancomycin is being increasingly used in medical centers with a high incidence of methicillin-resistant staphylococcal strains (39).

Therapy for established PVE is a different issue. Prior to the discovery of antibiotics, endocarditis was effectively untreatable. Since antibiotics predate valve surgery, there has always been a line of attack against PVE, however appropriate or successful. Antibiotic therapy remains the only real treatment option other than surgery, once PVE is established. Penicillin was the first antibiotic to be used successfully against endocarditis, but a much wider range of agents is now available for the treatment of the ever-increasing number of pathogens responsible. The choice of drug depends on the organism(s) isolated from the blood cultures, but frequently therapy must be started before the microbiological results are available. Even with early diagnosis and identification of the causative organisms, only about 40% of cases of PVE will not require surgical treatment (40-43). Surgical intervention is being increasingly performed at an early stage, with clinical and prognostic evidence to support this approach (44).

Unwanted side effects constitute a potential drawback of antibiotics, particularly when used in the high doses prescribed for PVE therapy. Even though antibiotics have been used for endocarditis for several decades, scant evidence-based information is available on optimum therapeutic regimens for this condition, and the tendency is to administer extremely high doses. This further emphasizes the need to minimize the incidence of PVE. It has been demonstrated that bolus doses provide higher drug levels in tissues than continuous infusions (45). Duration of therapy for PVE is another area that has little scientific evidence on which to base recommendations. At present, somewhere between four and six weeks seems to be the most accepted practice. It must be remembered that the risk of superinfection increases with the length of administration, particularly with broad-spectrum antibiotics. Fungal endocarditis is especially difficult to treat and has the poorest prognosis for recovery. Although amphotericin B has had limited success, surgical intervention is almost always required for cure of fungal infections, often at an early stage (19,46).

Wilson and Geraci provided recommendations for the antimicrobial treatment of PVE in 1983, and these have probably been the most widely adhered to (47). They emphasize monitoring for side effects, especially renal and auditory complications with aminoglycosides in the high doses suggested. It is important to establish whether the source of infection is intracardiac or extracardiac, and although guidelines have been published (20), there is no sure way to differentiate between these two potential sources of infections. Most clinicians will now make only one attempt to eradicate the infection medically before resorting to surgery. If

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surgery is indicated, antibiotics are continued for four weeks postoperatively.

Indications for surgery

These can be divided into relative and absolute indications, but in all cases the patient must be prepared for the possibility of explantation of the infected prosthesis, since sudden decompensation may warrant urgent surgical intervention (44). Failure of antibiotic therapy, as indicated by ongoing sepsis, and hemodynamic collapse or congestive heart failure are the most common of the absolute indications for surgery. Other absolute indications include obstruction of the valve, instability on echocardiography or radiologically, and new-onset heart block (19). Relative indications include embolic phenomena, mild paravalvular leaks and heart failure, non-streptococcal organism, vegetations and relapse. Fungal PVE is a difficult problem, with a mortality rate approaching 100% when using medical treatment alone. For this reason, most surgeons consider fungal PVE an absolute indication for surgery.

Masur et al. pointed out that all patients with PVE, except those with uncomplicated streptococcal infections, should be considered candidates for early surgery until proved otherwise (29,48-51). Since the mortality rate exceeds 75% in patients who have non-streptococcal PVE, aortic valve PVE, significant heart failure, or a new or increased murmur, early surgical intervention is most likely to be beneficial in such patients. Clearly, each individual case needs to be judged on its own merits as regards indications for surgery, and if so, the optimal timing for the operation must be decided.

Potential strategies for prophylaxis

Although PVE has traditionally been divided into the early and late forms at 60 days post implantation, actuarial studies have suggested that the risk of early PVE continues for 12 months (52). Since 'early' PVE has different etiology, pattern of disease and prognosis than 'late' PVE, these differences have implications for treatment and prophylaxis. Prevention of PVE is being more strongly emphasized, since morbidity and mortality are so high once infection is established. Nucleic acid typing techniques have helped to identify the etiology of the more common causative microbes, such as coagulase-negative staphylococci in early PVE, and with this information, a more specific approach to prophylaxis can be developed. It has become increasingly obvious that nosocomial bacteremia is a much more significant factor than has previously been accepted (53). Late PVE is traditionally 'prevented' by antibiotic prophylaxis during periods or events at risk for bacteremia. However, epidemiologic studies have shown these 'events' to be very unpredictable, and cannot be relied upon for appropriate prophylaxis of PVE.

Even with current perioperative antibiotic regimes, Gram-positive bacteria have been isolated in up to 10% of intraoperative blood cultures (54), and other microorganisms have been found in similarly large numbers, depending on the choice of antibiotic agents. The American Heart Association (AHA) and the British Society for Antimicrobial Chemotherapy have both published guidelines for prophylactic antibiotic regimens for patients with prosthetic valves undergoing interventive procedures, but the incidence of PVE remains worryingly high (55). This may reflect either the inadequacy of this form of prophylaxis in protecting against the development of PVE, or the lack of compliance of health care providers with these recommendations; for instance, one retrospective study found that compliance with guidelines was only 30% (56). The common discrepancies discovered included administration of antibiotics for procedures where it was not recommended, such as right and left heart catheterization, and choice of inappropriate antibiotics for procedures in which prophylaxis was recommended. Although adherence to guidelines is certainly one way of keeping the incidence of infection down, it is hoped that new strategies for prophylaxis may offer the best hope of achieving a significant reduction in the rate of PVE.

Antibiotic pre-immersion

Although this technique is practiced irregularly by many surgeons in a non-scientific manner, the correct use of this approach has been shown to reduce PVE substantially. Many contemporary surgeons immediately transfer the prosthesis to an antimicrobial solution once the valve container is opened, and soaking of the sutures in similar solutions is also practiced. Actis Dato et al. report on their use of a preimplantation immersion technique for more than 1,200 valves over 20 years (57). Their technique involved immersing the sewing ring in 50 ml of saline containing therapeutic doses of the same antibiotic as given at induction. The immersion was carried out immediately prior to implantation, and the general duration of immersion was 2-3 minutes. The operations were elective in 99% of cases, and all except two received mechanical prostheses. Systemic antibiotics were given routinely in all cases. Their incidence of early and late PVE were 0.08% and 0.95% respectively. However, this was a retrospective study using a combination of telephone, questionnaires and examination with a 76% response. It should also be noted that they administered parenteral antibiotics for four postoperative days, and the number of emergency cases was very low.

Although this technique of passive soaking may not

ide the full solution to PVE prophylaxis, it certainly suggests that some form of pretreatment of the sewing ring can be beneficial.

Prosthesis coating

Since biofilm formation reduces the effectiveness of systemic antibiotic therapy, there have been numerous investigations of the potential for modification or coating of the foreign surfaces for implantation. Among antimicrobial substances tested, silver has had promising results, having been used for several years against infection in dental, cardiovascular and orthopedic fields (58,59). It has recently been applied to prosthetic heart valves, with in vitro studies demonstrating effective broad-spectrum antimicrobial activity against *S. epidermidis, S. aureus, Streptococcus pyogenes, Klebsiella pneumoniae* and *Candida albicans*. This Silzone™ coating incorporates silver into the sewing cuff of St. Jude Medical® heart valves. A permanent dense layer of silver is bonded to each strand of the polyethylene terephthalate (PET) cuff fabric, using an ion beam-assisted deposition process. This novel sewing ring was shown to exhibit minimal leaching (dissolving or removal of the protective silver from the sewing cuff) under simulated in vivo conditions, and good biocompatibility (60). In addition, the concern of potential silver toxicity has been demonstrated not to be an issue in a 20-patient study. The valve has been tested in vitro using the NYS63 bacteriostatic activity test (61,62). Results showed a 99.13% reduction in the count of *S. epidermidis, Strep. pyogenes* and *C. albicans* counts on direct contact with coated fabric. Parallel streak tests showed some growth inhibition below the coating. Animal implant studies from the same group reported less inflammatory response to the silver-coated prosthesis when compared with the uncoated prosthesis. Scanning electron microscopy studies of silver-coated vascular catheters reported a reduction in platelet adhesion, although this finding has not yet been substantiated with silver-coated heart valves (63). Tripartite and ISO 10993 testing has confirmed no adverse changes in biocompatibility results from this form of silver coating. Clearly, any work involving modification of biomaterials needs to conform to such standards.

Although this form of slow-release antimicrobial impregnation appears promising, the lack of production of zones of inhibition by silver-coated prostheses may fail to provide protection against organisms embedded into the biofilm around the prosthesis. The antimicrobial silver compound is permanently attached to the sewing cuff, so only bacteria free of the exopolysaccharide slime that make intimate contact with the cuff are likely to be killed. The outcome of clinical trials are awaited for the silver-coated prostheses, but they have only recently begun to be implanted into humans, so interpretable results are some way off. A large, multi-center randomized, prospective study is planned for the near future.

Antibiotic/antiseptic impregnation of the sewing ring

It has been noted that PVE can develop in the presence of therapeutic serum levels of appropriate antibiotics. This is thought to be due to poor penetration of the drugs into infected areas. The sewing ring has been identified as the source of the majority of cases of mechanical PVE (64). The infection starts within the ring, then extends to involve the interface between the prosthesis and the annulus (65). Post-mortem studies have confirmed this area to be the site of initiation of infection in all cases of mechanical prostheses, most of which had vegetations on the prosthetic struts or cage (66). Since this interface is virtually unexposed to blood flow, even therapeutic serum levels of antibiotics are ineffective. The infection, if untreated, and frequently refractory to medical treatment, will continue to spread, resulting in the formation of abscesses, fistulas and generalized tissue breakdown. Post-mortem findings have concluded that the reason that some patients suffering from PVE did not respond to antibiotic therapy was due to extension of the infection into surrounding tissues (29,30,44). Clearly, if these stages could be avoided, particularly the deep-seating of infection within the sewing ring, then morbidity and mortality could be reduced. Slow-release, non-bioabsorbable bead systems have been successfully applied to prosthesis implantation in orthopedic surgery, but still require removal at a later date (67). This is obviously not a practical option in cardiac surgery.

Attempts to modify or protect the sewing ring were first introduced nearly 20 years ago (68), and developed to provide encouraging results for potential human use only as recently as ten years ago (69). These attempts sprung from the work carried out on prosthetic vascular grafts. Although topical treatment of prostheses had been attempted previously, the antibiotics tend to disperse early, and investigators had been looking for a way to seal in the drug. Olanoff et al. (68) described experiments incorporating gentamicin in silicone rubber within the sewing ring of mitral valve prostheses implanted into dogs. They were able to demonstrate increased survival rates with these systems. They showed that drug levels fell below therapeutic concentrations within two days, but had low-level sustained release for two months. This had very promising implications, suggesting that the correct combination of antibiotic and sealant may have great potential.

More recently, Karck et al. performed a series of

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experiments involving topical pretreatment of the sewing ring with a gentamicin derivative within a fibrin sealant (69). In vitro studies revealed constant antibiotic release from the ring for three weeks. When studied in a pig model, implantation of differently pretreated valves and deliberate staphylococcal inoculation resulted in some interesting findings. The sewing rings and corresponding implantation sites were assayed for antibiotic content after one week. Significantly higher quantities were found in both areas in the group pretreated with the gentamicin/fibrin sealant compound when compared with the group pretreated with antibiotic alone ($p < 0.005$). All groups without antibiotic pretreatment (control), and 90% of those with antibiotic treatment alone were found to be infected, whereas 50% of those pretreated with the antibiotic/fibrin sealant compound had sterile cultures.

Since these promising results, further work has been directed towards achieving high concentrations of antimicrobial agents in both local tissues and prosthesis without early dispersal, but there has been little clinical application to date. The elements required are adequate quantities of an appropriate antibiotic or antiseptic, and an effective method of maintaining its presence within and release from the prosthesis for a predetermined length of time. Clearly, early PVE is the subtype to be targeted by such an approach, since it would be impractical, if not impossible, to produce a prosthesis conferring antimicrobial prophylaxis indefinitely. Although the most common pathogens responsible for early PVE are staphylococci, it is preferable to impregnate heart valves with broad-spectrum antimicrobial agents that are active against superinfection.

Studies investigating sealed antibiotics in vascular prostheses have paved the way for applications in heart valves (70-76). French et al. passively impregnated the sewing ring of prosthetic heart valves for implantation into goats (77). The sewing ring was made of Dacron, and they used rifampin in both an unsealed state and after sealing by several methods, including autoclaving in blood or albumin. Their endpoints were assessment of anti-staphylococcal activity up to five days after implantation. The best results were obtained with the valves sealed with autoclaved blood. They also evaluated rifampin binding to gelatin-sealed (Gelseal) and collagen-sealed (Hemashield) Dacron products, and found anti-staphylococcal activity to be either negligible or absent by four days post implantation, although rifampin appeared to be better retained in gelatin-sealed than collagen-sealed material. Rifampin has a unique ability to bind covalently to an appropriate sealant for use in Dacron. This study also highlighted another potential problem for coated cardiac valves, namely the handling characteristics. Although pretreatment with autoclaved blood appeared to yield the best results in terms of sustained anti-staphylococcal activity, it rendered the sewing ring much more resistant to needle penetration. In contrast, the other coating techniques did not appear to affect the ease of needle penetration. It is important not to compromise these features, and future models will need to consider this carefully.

Cimbollek et al. have recently used gentamicin and clindamycin compounds for impregnation into sewing rings in a series of in vitro experiments (78). Pharmacokinetics and release profiles were extensively evaluated in vitro before in vivo testing, which demonstrated that clinically therapeutic levels of both gentamicin and clindamycin metabolites were obtained at the implantation site for at least two weeks. Garrison and colleagues have since reported on rifampin bound to prosthetic vascular grafts in high concentrations, and evaluated the effects in vitro and in vivo (79). In vitro, all of the tested concentrations of rifampin produced near-total killing of low inoculas of slime-producing bacteria, but not the high inoculas. They found that resistance developed in all cases with high initial bacterial biofilm formation. The in vivo experiments established an optimal concentration which achieved a balance between killing efficiency and prevention of resistance. They also found that when systemic vancomycin was added, bacterial clearance was slightly improved, but there was no effect on rifampin resistance developing in the presence of high bacterial inoculas. They concluded that the routine use of antibiotic-bonded grafts should be discouraged in non-infected cases for fear of resistance developing.

Although there are only a limited number of reported studies, further work on antibiotic/antiseptic-impregnated sewing rings is currently in progress. Slow but effective release of antimicrobial agents from the impregnated valve, resulting in effective zones of inhibition against all potential pathogens, is the ultimate goal of producing an anti-infective heart valve. Using this specific approach, central venous catheters coated with antibiotics or antiseptics have been demonstrated in prospective, randomized, multi-center clinical trials to reduce significantly the rates of catheter colonization and catheter-related bloodstream infection (80,81). Therefore, it seems likely that this antimicrobial coating approach, above all others, may hold the key to dramatically minimizing the incidence of PVE.

Biofilm modification

Bacteria that form around and thrive upon the environment of artificial surfaces or implants all form a slime-enclosed biofilm, which protects them to varying extents from antibiotic activity (82). It is now widely

cepted that this is the reason for the remarkably stubborn resistance of implant-related infections to even intensive antibiotic therapy. It has been demonstrated that biofilm bacteria are resistant to many antibacterial agents at levels 500 to 1,500 times the concentration required to kill the same freely circulating organisms. Furthermore, biofilms more than seven days old are resistant to 500 to 5000 times the concentrations required to kill the free-floating cells of the same organism. The mechanism of this resistance was not well understood at first, but was thought to be due to limitation of diffusion by the polyanionic matrix layer and on phenotypic adaptations to biofilm growth that alter the metabolic targets of the antibacterial agents. It has clearly been shown that placement of an artificial device that has been colonized with a bacterial biofilm before implantation will always cause a device-related infection, regardless of administration of systemic antibiotics. This is an important concept to appreciate, when considering new approaches to prevent deep-seating of infection in cardiac prostheses.

As more is being understood about biofilms, and their effects on artificial implants, this knowledge is being used for beneficial effects. Most of the initial work has investigated biofilms on intravascular heters and orthopedic implants, but there is no reason why the findings to date cannot be translated for use in the cardiac environment. The concept of 'slime' and its sealant effects when coating vascular implants has been recognized for some time. Slime-producing bacteria can colonize these intravascular devices, and when they are embedded in biofilm, they are shielded, and become resistant to a number of antibiotics (83). It is this coat that needs to be penetrated if successful eradication of infective agents is to be achieved. There have been several in vitro models to demonstrate antibiotic penetration of the biofilm produced by various slime-producing organisms, including coagulase-negative staphylococci (84). It has been concluded from these experiments that failure of vancomycin to cure prosthetic infections is likely to be due to the diminished antimicrobial effect on bacteria in the biofilm environment (because of the low growth rate of bacteria within the biofilm, and/or inactivation of antibiotics by the biofilm material), rather than poor penetration of vancomycin into the biofilm itself.

Khoury et al. have discovered that the resistance of biofilm bacteria can be eliminated with the aid of an electrical field (82). Weak fields (150 $\mu A/cm^2$) applied to the biofilm enormously enhance the penetration of ibiotics and killing of bacteria. Their initial experiments used a DC field similar to that used to promote bone healing and tissue repair, but weaker than that used to kill free-floating organisms by electrical activity alone. Several studies have confirmed the killing of bacteria by electrical means alone, attributing this to iontopheresis, but requiring larger-strength fields (85,86). Using the knowledge that electric fields and currents can influence the organization of biological membranes, Khoury and colleagues combined the electrical attenuation of the biofilm with the administration of antibiotics. Their data showed that the normally highly resistant biofilm bacteria were killed on all steel surfaces within the flow cell in the presence of tobramycin, including non-electrodes. Electrically assisted electrophoresis results in an enhanced bioelectric effect with antibiotics, and helps carry these agents through the biofilm matrix. A number of bacterial species appeared to be susceptible to the effect, and most antibiotics tested were compatible, regardless of the mechanisms of action.

Work continues to progress in this field and, as understanding broadens, it greatly increases the implications for use of these principles in the manufacture of heart valves.

Summary

Prosthetic valve endocarditis is a devastating consequence of what is usually successful and life-changing surgery. Although the incidence is reportedly between 1 and 5%, the high morbidity and unacceptable mortality rates (perhaps as high as 70%) demand new approaches for prevention. It has recently become clear that antibiotics are largely ineffective in treating established PVE. The answer is, therefore, in prophylaxis, and several different avenues have been explored. The most promising solutions are likely to be some form of coating or impregnation of the sewing ring with antibiotic or antiseptic agents. Appreciation of the resistance of biofilm bacteria is also very important, and it is paramount that this knowledge is incorporated into new preventive techniques. Results of studies to date have only represented laboratory conditions, and it will be some time in the future until we can assess significant clinical data. In the meantime, it is important that ongoing studies attempt to reproduce the unique environment found in the living human body. Our concerns are that many of the studies to date have tested against 'laboratory-bred' strains of the common pathogens, which may not be as resistant as those found in practice. Furthermore, there is an enormous difference between the free-circulating, or planktonic, bacteria usually targeted experimentally, and the biofilm bacteria that are more likely to be encountered clinically.

Nonetheless, it is the authors' impression that research in this area is extremely encouraging, and that a validated and efficient method of prophylaxis against PVE, with subsequent reduction in morbidity and mortality, is close to being established.

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