CHAPTER 3

ARTIFICIAL IMPLANTS – NEW DEVELOPMENTS AND ASSOCIATED PROBLEMS

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Abstract: Implanted short-term and long-term medical devices have been exhibiting extreme promises in promoting quality of life while increasing life expectancy of affected individuals. The risk of bacterial infections associated with open surgery or the implementation of these devices remains to be a major drawback. The primary causes of infections associated with medical devices are Staphylococcus epidermidis and Staphylococcus aureus. The two potential interventions to bacterial infections associated with medical devices include the development of materials that could discourage bacterial adherence and exhibit antimicrobial activity. The preventional methods ranged from the development of anti adhesive polymers comprising the implant to impregnating implant cements with antibiotic devices that extend the therapeutic response due to slow release effect. New areas of implant research include the use of liposomal antibiotics as coatings for implants. In this communication, we will review the chemical nature of commonly used implants, the source of infections, as well as the preventional measures of coatings and the antibiotics employed to reduce infection due to different implants and medical devices

Keywords: artificial implants, infections, bacteria, antibacterial, anti-adhesion, antibiotics, polymers, IRI, implant coating, biomaterials, bone cements

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M.R. Mozafari (ed.), Nanomaterials and Nanosystems for Biomedical Applications, 53–65.

1. INTRODUCTION

The integration of artificial implants in biological environments is an outstanding advancement in medicine that allows for increased mobility, improved sight, as well as enhanced delivery of food and drugs. Although this vast range of artificial implants can improve the quality of life by restoring compromised physiological functions, they may also carry such health risks as biocompatibility and microbial infections that impede a successful implantation.

Microorganisms may cause device-related infections by: a) colonizing the implant through direct inoculation at the time of implantation; b) reaching the implants by hematogenous seeding during bacteremia or; c) through direct continuous spreading from an adjacent infectious focus. Infections caused by Staphylococcus epidermidis and S. aureus are more common, making up some 70–90% of the implant related infections [1]. Some serious complications of implant-related infections include: abscesses, endocarditis and septicemia [2]. Infections caused by these bacteria generally are preceded by protein adsorption [2] onto the surface of implants and the resultant "film" formation that supports bacterial adherence and colonization.

Aseptic techniques and decontamination of the surgical site are common prophylactic approaches to infection. In addition, a relatively new approach to reduce the risk of microbial infection and inflammation due to an artificial implant involves the coating of the implants with free- or encapsulated- antibiotics in lipids (i.e. liposomes) or polymers. Such alterations in implant composition should preserve the implant integrity while allowing its integration into the host system and diminishing adverse reactions.

In the following paragraphs, we will review recent developments in several medical implants that have had profound impact on modern medicine. We will also elaborate on the potential bacterial contaminations of particular implants and the new approaches to address the infection and inflammation problems. The specific implants that will be dealt with include dental implants, catheters, stents, orthopedic implants, intraocular lenses, as well as skin grafting. Finally, we will briefly discuss the implications of respiratory and cardiac implants and related complications.

2. DENTAL IMPLANTS

Dental implants provide a restorative tool to support crowns, bridge abutments, and removable dentures. Osseointegrated implants are titanium posts that are surgically implanted in alveolar bone. A tight immobile bond (osseointegration) forms between bone and titanium, and prosthetic and restorative fixtures are attached to the implants. Titanium implants differ from natural teeth, which may make them more susceptible to mechanical stress. Small proportions of implants are not successful and may fail due to infection. Bacterial adhesion on titanium implant surfaces has a strong influence on healing and long-term outcome of dental implants. Reducing the risk of infection is particularly more important and often more difficult to accomplish because the mouth is exposed to many unsanitary conditions. Two of

the most common sources of infection in dental implants are Streptococcus mutans and Streptococcus sangus [3]. Streptococci and Actinomyces species appear to be the initial colonizers of artificial dental implants and plaque formation. Attachment of these microbes, in turn, encourages other anaerobic bacteria including Fusobacterium, Capnocytophaga, and Prevotella to invade and colonize dental implants resulting in periodontitis [3].

Dental implants are available in different shapes and materials with diverse surface characteristics to enhance their clinical performances. For instance, titanium implants appear to resist the adhesion of the primary colonizers Streptococcus mutans and Streptococcus sangus. Modification of titanium implant surfaces by titanium nitride (TiN) or zirconium nitride (ZrN) coatings may further reduce bacterial adherence and improve their clinical performance [3]. Studies on the effect of different surface treatments of titanium implants employed in oral surgery emphasized the importance of interactions between microbes and implants. For example, highly polished titanium surfaces tend to discourage bacterial adhesion [4] but their usefulness is restricted because the polished neck of dental implants does not osseointegrate as do textured surfaces. Likewise, titanium implants coated with a hard ceramic resulted in a moderate reduction in plaque formation [5]. An implant with titanium zirconium-oxide on the ondosseous section with titanium-niobium-oxinitride covering the supragingival area indicated antimicrobial and anti-adhesion properties while was very resistant to wear [6]. Generally speaking, titanium alloys appear to be more effective on inhibiting plaque formation because they hide the highly reactive surface of the titanium.

The role of antibiotics in reducing dental implant related infections have been investigated as well and it was found that Tetracycline (TC) is an effective and widely used antimicrobial agent against periodontal infections for several reasons. These include: i) TC has the ability to delay plaque formation and to reach and react towards root surface bacteria; and ii) TC exhibits anti-collagenase activity, hence works against a wide variety of periodontal bacteria [7]. The antimicrobial effects of antibiotics impregnated into a polyurethane dental implant have been reported against Porphyromonas gingivalis. The antibiotic is released and starts working as soon as the bacterial enzyme begins degrading the implant. The use of biodegradable polymers such as poly (-hydroxybutyrate-co-hydroxyvalerate) PHBV and PVA (polyvinyl alcohol) incorporated TC are more attractive because they negate the necessity for a second surgery to remove the capsules or sphere. Although considerable advances have been made to improve the applications of dental implants in the context of bacterial infection, more research is needed to effectively reduce or even eliminate bacterial infections associated with these medical devices.

3. CATHETERS

Catheters are used in a wide range of applications varying from urinary catheters implanted for relatively short periods to venous catheters that are permanent at times. As with all medical implants, one of the major complications is microbial

infections that result from bacterial adhesion to the catheters. More than 150 million venous catheters are utilized every year in the USA alone, with a contamination rate of approximately 4% [8]. Catheter-related infections of the venous system are often referred to as CRBIs (catheter related bloodstream infections). Majority of CRBIs are caused by the organisms that colonize the skin (70–90%). These bacteria are primarily responsible for short-term infections. Long-term infections (those persisting for longer than 8 days), however, are primarily caused by the bacteria of the lumen where the catheter is implanted. As with many implants, the most common bacteria responsible for catheter-related infections are Staphylococcus aureus and Staphylococcus epidermidis. The initial bacterial adhesion to the surfaces of implants is generally directed by van der Waals forces, electrostatic interactions, and by hydrophobic interactions between bacterial membrane components and biomaterial surfaces [9, 10]. Bacteria can also adhere to catheter surface more strongly by methods other than the ones indicated above. For example, S. aureus and S. epidermidis express adhesin receptors that strongly bind to the glycoproteins, collagen, or laminin of the extracellular matrix surrounding the implant [11]. The stronger binding of S. aureus to the extracellular matrix materials surrounding the implants is attributed to the expression of more adhesin receptors compared to that of S. epidermidis [12].

There are two main strategies aimed at preventing catheter-related infections. One is the creation of anti-adhesive biomaterials and the other is the incorporation of antimicrobial or antiseptic agents into the polymer matrix. Of the materials used for catheter construction, plastic catheters have a higher rate of infection than the steel [13]. Common plastic materials used in catheters are polyvinyl chloride (PVC), Teflon, siliconized latex, poly urethane, and Vialon. Studies indicated that PVC and siliconized latex show significant bacterial adhesion, while polyurethane exhibits the best anti-adhesive properties [14, 15]. Teflon coating on catheters have been shown to reduce bacterial colonization, but one problem with Teflon is that it doesn't stick well to the polyurethane, a common composite of catheters [16]. It is also shown that implant matrices containing heparin or polyurethane oxide have better anti-bacterial adhesive properties [17]. Like wise, the use of a heparin coating, when attached to the IV catheter via benzalkonium chloride, proved very effective as an anti-bacterial adhesion agent [18]. Silver/collagen cuffs were also proposed as a coating for central venous catheters, but the research showed no reduction in the incidence of infection [19]. Although silver is a good antibacterial agent, serum components such as albumin renders it inactive by binding and precipitating it. A catheter coating composed of exidine and silver sulfadiazine, however, reduces short-term venous infection [20]. A possible explanation is that the silver compounds resist or reduce the precipitation of silver by serum proteins.

Other coatings used to reduce catheter infections include steryl polyethylene oxide-co-4,4'-methylene diphenyl diisocyanate-co-steryl polyethylene oxide (MSPEO) and chitosan, both of which are bioabsorbable and bacteriostatic. MSPEO works well against bacteria because it does not adsorb plasma components due to its steric repulsion, but it has problems forming stable attachment on implant surfaces.

Chitosan, on the other hand, attaches well to catheter materials and can tightly be incorporated with bacterial cell wall, but is slightly haemostatic [7]. Combination of the two products referred to as chi-MSPEO, however, proved to be a less toxic and effective anti-bacterial coating that adheres well to polyurethane catheters [21]. Thrombosis, a major concern associated with catheterization of the venous system, was absent in the studies using this mixture.

Antibiotics coated catheters have been investigated in catheter related infections. This is an attractive approach because of their expected rapid and local antibacterial effects. However, this approach is often problematic because the antimicrobial drugs elude from the catheter too quickly, hence do not exhibit prolonged bacterial inhibition. To address this problem, tridodecylmethylammonium chloride (TDMAC), a cationic surfactant, was used to coat the catheter and was shown to greatly increase retention of anionic antibiotics [22]. In this study, several antibiotics and antimicrobial agents including cefazolin, teicoplanin, cancomycin, silver, chlorhexidine-silver sulfadiazine (C-SS) and minocycline-rifampin (M-R), were investigated for their ability to inhibit bacterial colonization on these catheters. The data indicated that cefazolin conjugated to catheter with TDMAC and C-SS showed the lowest amount of colonization (2.1% and 2% respectively). The highest degree of colonization was seen in silver impregnated catheters (45.1%) and vancomycin conjugated with TDMAC (62%). A significant advantage of C-SS and M-R coated catheters is that they do not evoke antimicrobial resistance in bacteria [23, 24]. Hence, the Hospital Infection Control Practices advisory committee recommended the short-term use of these catheters [25].

Several investigators have also explored application of liposomal antibiotics in prevention of catheter-associated bacterial infections [26]. Application of ciprofloxacin encapsulated in DPPC-PEG-DSPE (Dipalmitoyl phosphatidylcholine – polyethylene glycol – distearoyl phosphatidyl ethanolamine) – gelatin liposome formulation on a silicon catheter completely eliminated bacterial adhesion and effectively inhibited the growth of Pseudomonas aeruginosa [26]. The liposomal antibiotic coating showed a slow but constant antibiotic release over a 94 hour time period. The hydrogel that shielded liposomes during insertion was composed of gelatin nitrophenyl carbonate activated PEG. Likewise, application of rifampicin entrapped in a PDMS-based polyurethane (PU) grafted with monomethoxy polyethylene glycol (MPEG) minimized catheters-associated urinary tract infections. The data indicated a great repulsion of E. coli and S. epidermidis adherence. The drug release kinetics showed a gradual release of rifampicin from the PU-MPEG coatings for 45 days. This slow release of the antibiotic retains an adequate concentration of the drug at the sites of infection and eliminates the need for the frequent systemic antibiotic therapy and reduces drug toxicity as well [27].

Urological stents coated with antibiotics encapsulated in polymers have also been tested in the context of catheter-associated infections. For instance, studies by Multanen et al [28] indicate that ofloxacin coating bioreabsorble self-reinforced L-lactic acid polymer (SR-PLLA) reduces bacterial adhesion with the exception of E. faecalis, which is naturally resistant to ofloxacin. A liposomal ciprofloxacin

containing hydrogel for external coating of silicone Foley catheters has been developed by Pugach et al [29]. This particular coating offered several advantages in rabbits catheterized with liposomal ciprofloxacin hydrogel coated catheters compared with untreated controls [29]. For instance, catheters coated with liposomal encapsulated ciprofloxacin hydrogel showed a significant increase ($p = 0.04$) in protection from the development of bacteriuria compared to controls (untreated or hydrogel coated) and increased median time (from 3.25 days in untreated catheters to 6.25 days treated catheters) to development of bacteriuria in rabbits. Recently, Schinabeck et al [30] developed a rabbit model of catheter-associated infection with C. albicans biofilms and showed that antifungal lock therapy with liposomal amphotericin B is an effective treatment strategy for such infections. In this study a silicone catheter was surgically placed in New Zealand White rabbits and animals were infected with C. albicans and treated with saline (untreated controls), liposomal amphotericin B lock, and fluconazole lock. Quantitative cultures revealed that catheters treated with liposomal amphotericin B yielded 0 cfu, which was significantly better when compared to the untreated controls ($P < 0.001$) and the fluconazole-treated group ($P = 0.0079$) [30].

Chronic urinary catheters exhibit even greater problems with an infection rate of nearly 100% [31]. Phosphorylcholine (PC), an effective anti-thrombotic IV catheter coating, drastically reduces adsorption of fibrinogen to implant surfaces. This, in turn, discourages adherence of several bacterial species including S. aureus [13], E. coli, and Proteus mirabilis adhesion to the urinary catheters. In summary, many advances in different fronts have been made in an effort to reduce catheter-associated bacterial infections and the resultant morbidity and mortality. However, more work needs to be done in this area to completely eradicate the problem. Towards this end, a possible solution would be to develope controlled release formulations of antibiotics designed specifically for catheter coating.

4. STENTS

Medical stents are designed to maintain the lumen of a body tube and are commonly used instead of or along with angioplasty. Stents, the hollow cylinders that keep the lumen open, are very useful devices but have their own share of problems that may result in rejection of the implant. Restenosis is a serious problem with stent implants as they can completely close off the opening that was maintained by stents. In addition, stents can develop post insertion infections, which will result in removal of the device and may increase morbidity and mortality. The review of recent publications reveals several approaches to minimize bacterial colonization of the stent. Coating of the stents with liposomal antibiotics proved to be effective therapeutic measures as they are for urinary tract catheters.

Hydrogels can be used to cover metallic stents for controlled drug release and gene transfection. A photoreactive material consistingof a gelatin macromer (multiple

styrene–derivatized gelatin) and carboxylated camphorquinone (photo-initiator) can be used as the coating material. A few minutes of visible light irradiation of a stent after dip-coating of an aqueous solution of the photoreactive material results in the formation of a homogeneously cross-linked gelatinous layer on the entire exterior surface of the metal stent. Rhodamine-conjugated albumin as a model drug or the adenoviral vector expressing bacterial beta-glactosidase (AdLacZ) as a model transfection vector was photo-immobilized in the gelatinous layer. Results showed effective gene transfection and drug release from gel after three weeks of implantation [32].

Another stent used for study was composed of polytetraflouroethylene (PTFE) and coated in liposomes containing PC (phosphatidylcholine) and CHOL (cholesterol). This liposomal coating showed that less than 30% of the liposome remained attached to the stent 72 hours after preparation. Upon incubation of the same composite in urine, $50 \pm 5\%$ of the drug was released from the stent over a 48 hour time period [33]. These release kinetics can be found to be beneficial in preventing infection associated with urinary stent implantation. Medical stents are very important in maintaining functional passageways for constituents of the body and there are a wide variety of coatings used on a wide variety of stents to ensure integration in the biological system. Much of the research described, however, only show effective results over a relatively short period of time (less than three weeks). Therefore, more long-term studies are clearly needed to prolong the presence and effectiveness of antimicrobial drugs in the body as stents are often left in the body for very long periods of time.

5. ORTHOPEDIC IMPLANTS

Orthopedic implants are the most widely utilized and researched medical devices. Their applications range from hip and knee replacement to cranial implants. These implants are of particular concern and often exhibit the largest risk of rejection and removal because they are generally much larger than other medical implants. For instance, acute infection and chronic myelitis occur in 5 to 33% of the open fracture implant replacements [34, 35] and 1 to 3% of orthopedic surgeries [36]. Studies indicate that most total knee and total hip arthroplasty patiens (58%) with surgical site infections (SSI) develop post-surgery deep wound infections (DWI). Hematoma and post-operative drainage appear to increase SSI [37]. Financial burden of post-surgical infection-related complications in the USA alone is about \$ 3.4 x 10^8 per year. S. aureus is isolated in 90% of primary abscesses while Gram negative bacteria comprise 10 to 20% of the implant related infections [38]. E. coli is the most common cause of secondary infections followed by Enterobacteriaciae and P. aeruginosa. New advances in materials used in cranial implants include the use of hydroxy appetite cements (HAC). Hydroxy appetite (HA) comprises 80 to 90 % of the calcified skeletons [39]. Hydroxy appetite cement, however, is a better

alternative to ceramic HA because it hardens within the body instead of being done in the lab. The best use for HAC appears to be the skull implants because of its biocompatibility and that it requires no special tools (i.e. screws, micro plates, etc.) for integration into the skull [40]. Furthermore, HAC is osteoconductive, infection resistant, and adheres well to the surrounding bones.

As previously mentioned, microorganisms such as S. aureus, S. epidermidis, Enterobacteriaciae and P. aeruginosa are commonly associated with orthopedic implants. Early treatments of these infections include the systemic administration of antibiotics cefazolin and ciprofloxacin or gentamicin and penicillin G to manage Gram–positive and Gram–negative bacteria, respectively [34]. The systemic antibiotic therapy is relatively effective, but as mentioned earlier, requires more frequent administration and higher dosages that could result in drug toxicity. In addition, one of the biggest problems associated with orthopedic implants is the production of antibiotic impermeable biofilms around the implant. Biofilms are produced by bacteria and often result in the removal of the implant in order to cure the infection. An effective and alternative antimicrobial approach is the use of antibiotic loaded polymethyl methacrylate (PMMA) beads at the infection sites [41]. Several drawbacks are associated with the application of the polymeric beads [34–42]. These include inadequate antibiotic concentration that may result in antibiotic resistant strains and the fact that PMMA is not biodegradable and therefore requires a second surgery to remove the beads. However, coating of stainless steel implants with gentamicin encapsulated in the biodegradable polylactide–co–glycolide (PLGA) showed an optimum release kinetic and maintained adequate levels of antibiotic for three weeks. This antibiotic carrier system eliminated infections caused by S. aureus at the implant site [41].

Other research groups have employed antibiotic carrier systems composed of less biodegradable materials that mimic the structure and functions of bones. These include calcium phosphate gelatin (with a Ca/P ratio of 2.3) impregnated with gentamycin, which showed an initial burst of antibiotic release followed by an essentially constant release for 3 months in vitro [43]. However, upon implantation into rabbit tibia the release duration was substantially shortened to about 4 weeks. This shortening of gentamicin release was attributed to the degradation of gelatin. Histological findings showed that this bone composite was biocompatible as no chronic lymphocytic infiltrates nor areas of macrophages or foreign body giant cell formation observed, therefore, this formulation may have a great potential as a bone substitute material [43].

Finally, Yagamurlu and co-workers [44] utilized a conjugate composed of the biodegradable material poly (3-hydroxybutyrate -co-3- hydroxyvalerate) (PHBV) and sulfactam-cefoperazone to inhibit the growth of S. aureus. This treatment was very effective in inhibiting bacterial growth and in the prevention of implant-related osteomyelitis (IRO). Despite the advances outlined above, more work needs to be done as no universal composite has been developed that could be utilized with regard to many problems that are associated with orthopedic implants.

6. LENSES

Bacterial contaminations of lenses during or after surgery are extremely important because infection-related complications could result in blindness. One study showed that the PC coating of an intraocular lens (IOL), composed of silicone, decreased adherence of S. epidermidis by 20–fold [45]. A further 20–fold decrease in adhesion of the bacteria was achieved when the IOLs were composed of PMMA. Heparin has also been used for coating the silicone IOLs. These heparin modified silicone (HMS) lenses display a 15–fold reduction in silicone oil adherence, which has been linked to the presence of vitreoretinal disease [46]. As for PMMA lenses, heparin coating resulted in a significant decrease in adherence of S. epidermidis, which can cause implant-associated bacterial endophthalmitis [47]. The coating of intraocular lenses has also been proven to reduce inflammation in and around the eye [48].

7. SKIN GRAFTS

Skin grafts and tissue repairs are becoming a common practice in modern medicine. The fragile nature of the skin and tissues, in comparison to implants, and the important protective role of the skin in infection and inflammation are challenging aspects of these operations. As for infection control measures, liposomal delivery systems have been utilized to prevent infections and expedite healing process [49, 50]. For instance, polyvinyl-pyrrolidone-iodine liposome hydrogel improves wound healing by a combined moisturizing and antiseptic action, when compared to conventional antiseptic chlorhexidine [49]. Encapsulation of silver sulfadiazine (SSD), the drug of choice for topical treatments of infected burns, has also improved its efficacy by allowing a slow release of the antibacterial drug over 24 hours [50]. As with other implants, the use of antibiotic grafted polymers have been proven to be far more effective than traditional methods in preventing infections and accelerating tissue repair.

8. RESPIRATORY IMPLANTS

Intubation or implantation of artificial devices into the respiratory system are often necessary in order to overcome respiratory problems ranging from ventilation of a defective lung to intubation of a newborn with immature respiratory system.

The most common types of respiratory implants, however, are endotracheal tubes (ET). ETs allow oxygenation and positive pressure ventilation, but prolonged post-surgical procedures are associated with bacterial infections and increased mortality [31]. Introduction of the patients own throat flora during endotracheal intubation and exposure of the secretion pool around the tube cuff to nosocomial microbes are the major risk of pneumonia in intubated patiens [13]. P. aeruginosa is one of the commonly encountered and recognized bacteria associated with respiratory intubations [51]. The following measures are suggested to reduce infections related to catheters and ETs:

1) Anti infective coated catheters: Polyurethane catheters that are impregnated with minute quantities of silver sulphadiazine and chlorhexidine indicated a significant reduction in catheter-related infections in clinical trials. Hexetidine may prevent infections by biofilm forming bacteria as it has anti-plaque forming activity [52]. Likewise, preclinical studies with silver hydrogel coated ETs exhibited a significantly longer onset time for P. aeruginosa [51].

2) Antibiotic coated catheters: Several antibiotic coated catheters including minocycline-rifampin-coated catheters have proven to be superior to antiseptic coated catheters because, unlike the older types of antiseptic catheters, both external and internal surfaces of the catheter are coated. In addition, the combination of minocycline and rifampin exhibits superior surface activity against staphylococci [24] versus chlorhexidine-silver sulphadiazine. The use of higher concentration of chlorhexidine-silver sulphadiazine on the external and internal surfaces of the catheters is now being evaluated in a multicenter trial [25]. The major theoretical drawbacks with antibiotics coated catheters are: a) the ineffectiveness of antibiotics against antibiotic-resistant bacteria and yeasts; b) the risk of promoting bacterial resistance with long-term topical use; and c) risk of hypersensitization. Future studies are needed to evaluate the impact of anti-infective-coated devices on the emerging nosocomial bacterial resistance [26–28]. Avoiding the risk factors that increase the need for prolonged intubation or reintubation will reduce the risk of infections associated with intratracheal catheters.

9. CARDIAC IMPLANTS

Another development in the area of artificial implants is the replacement of heart components with artificial devices, primarily pacemakers and prosthetic cardiac valves. These devices serve to maintain cardiac function without the need for total heart replacement. These techniques greatly reduce the risk of immunological rejection, but bring with them the risk of infection. Endocarditis and sepsis are two very unfavourable and potentially lethal complications associated with cardiac valve replacement. Prosthetic valve endocarditis (PVE) occurs in 0.5–1% of the operations with a high mortality rate of 50% [53, 54].

A treatment modality for PVE is designed and patented by the St. Jude Medical Inc. It is a silver-coating sewing ring commercially known as Silzone®. The Silzone® incorporates silver to Dacron implant fibers in an effort to utilize antimicrobial activity of silver without leaching into the cardiovascular system [55]. The Artificial Valve Endocarditis Reduction Trial (AVERT) was then designed to evaluate the efficacy of the Silzone® in reducing PVE in the absence of the concerned device-associated thrombosis. Although the study confirmed Silzone's anti-PVE activity in the absence of thrombosis, it revealed a higher rate of paravalvular leakage in the Silzone® study arm [54]. Consequently, this device was debunked, but the concept has since been evaluated by others with mixed results [56–58].

Infections of prosthetic heart valves generally occur at the sewing cuff-tissue interface [59]. In vivo efficacy of antimicrobial-fabric impregnated with

minocycline-rifampin or direct coating of the prosthetic heart valves with these antibiotics has been confirmed against S. aureus and S. epidermitis [58, 60]. Likewise, studies by other investigators indicate that the coating of the cardiac valve prevents infections caused by S. epidermidis (with a greatest inhibition), S. aereus, E. faecelis, P. aeruginosa, and Candida albicans [60]. The broader spectrum of MR antimicrobial activities and the fact that the combination therapy will less likely select resistant strains comparing to that of rifampin alone make the MR approach more attractive.

Fungal endocarditis associated with valve replacement is a rare but potentially dangerous complication with 8% fatality rate [27]. Common causative agents include C. albicans, Aspergillus, and C. parapsilosis [61–63]. Systemic applications of liposomal amphotericin B along with flucytosine are effective treatment modalities. Direct application of these antibiotics on prosthetic cardiac valve appears to be another option but there is no data available at this time [64, 65].

10. CONCLUSIONS

As this paper has shown, there has been a great deal of work on the developing new and better implant composites as well as many coatings, rods, spheres, beads and separate implants that attempt to ward off bacterial adhesion and to act as bacteriocidal. These implants range from the skin to the teeth to joint replacement and even the repair of skull defects and the replacement of intraocular lenses. The trend in these materials is to develop new, better, and more cost effective biodegradable polymers that will allow for slow absorption of the material by the body thereby negating addition invasion procedures to remove part or all of the implants. Much research has also been done on the bacteria and microorganisms causing the infection; and often eventual removal of implants is required to find the best strategies to fight these microbes. Although a great deal of work has been done in the area of medical implants, there is no device or technique better than simple sterility during an operation and still no practice of implant preparation to completely eliminate the existence of infection in a surgery as invasive as implantation of a foreign device. Consequently in the end it can be said that although the research community is close to finding the perfect device and materials and antimicrobials for implantation, more research is left to be done in hope that implantation related infections could be completely eliminated.

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