Review Article

Penile prosthesis biofilm formation and emerging therapies against them

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Abstract: Infections are among the most feared and devastating complications of penile prosthesis infections, often requiring surgical exploration and explantation are prosthesis infections. While the rate of infections have decreased due to antibiotic prophylaxis, antiseptic device preparation, increased sterility in implantation techniques and device modifications, infections still occur at a rate of 1–3%. This article reviews the formation of biofilms on penile prostheses and novel, experimental methods to prevent and eradicate them.

Keywords: Adult; biofilm; infection; penile prosthesis; treatment

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Introduction

Erectile dysfunction (ED) affects up to 152 million men worldwide (1). Current treatment options include oral phosphodiesterase-5 (PDE-5) inhibitors, intraurethral pellets, intracavernosal injections (ICIs), and penile prosthesis placement. Of these treatments, PDE-5 inhibitors remain the first-line option due to their efficacy and safety (2). Intraurethral pellets and ICIs are considered second-line therapies, while prostheses are considered definitive interventions as patients undergoing inflatable penile prosthesis (IPP) placement are either unable to tolerate, non-responsive, or refuse the aforementioned treatment options (3).

Although more expensive than their non-mechanical counterparts, IPPs offer a durable, concealable, and reliable mechanism for obtaining the rigidity necessary for intercourse with 15-year revision-free survival and satisfaction rates as high as 59.7% and 98%, respectively (4). Despite the advantages, analysis of Medicare claims data from 2001 to 2010 shows decreasing utilization of IPPs (1). Lee *et al.* (1) identified a 50% decrease in utilization of IPPs across all demographic factors, such as age, ethnicity, and geography, despite a 165% increase in the incidence of ED. This decrease has occurred despite increasing public awareness of ED. However, direct-to-consumer marketing may have led to the higher relative use of medical therapy over prostheses placement in treating less severe ED (5). Interestingly, when IPPs were used, the surgeries were more likely to be performed on sicker patients with significantly more comorbidities (1). This finding may reflect the sicker patients' inabilities to respond to medical therapies. The increasing burden of comorbidities carries with it higher rates of intraoperative and postoperative complications (6,7).

One of the most feared complications of IPP placement is infection, often requiring device removal. Antibiotic prophylaxis, antiseptic device preparation, improved implantation techniques and device modifications have reduced the rate to 1–3% (8). Contamination of the implant prior to or during the operation leads to planktonic

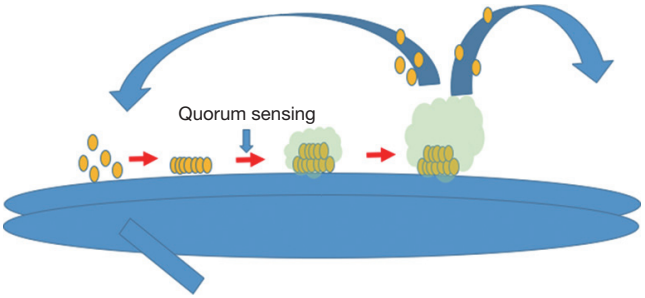

Figure 1 Four-step development of biofilm: (I) attachment of planktonic cells; (II) aggregation/accumulation of planktonic cells to form monolayer and microcolonies; (III) maturation; and (IV) detachment and dispersion.

organism proliferation and potential biofilm formation (9). Biofilms are colonies of bacteria or fungi that are capable of forming on variable surfaces such as *in vivo* medical devices, pipes and teeth. They can form on abiotic surfaces within 16 hours of device placement and insulate the causal organism from host immunologic defenses and antimicrobials (10,11). Additionally, biofilms enhance microbial survival by reducing bacterial growth rate and promoting antimicrobial resistance, damage surrounding tissues, and trigger inflammation (12). In this article, we review factors contributing to biofilm formation on IPPs and novel methods to prevent and eradicate them.

Microorganisms that form biofilms on penile prostheses

Advancements in implant technology and antiseptic device preparation have decreased infection rates to approximately 1–3% in recent years (13). The two producers of 3-piece IPPs in the US have developed infection-retardant coatings on their implants to reduce infection rates. Boston Scientific (Marlborough, MA) uses a coating of rifampin and minocycline called InhibiZone®. Coloplast Corporation (Humlebaek, Denmark) coats its devices with polyvinylpyrrolidone, a hydrophilic substance that absorbs the antibiotics the IPP is bathed in immediately prior to implantation (10). In a large observational study comparing the infection rates of 1,944 non-coated to 2,261 InhibiZone®-coated IPPs, Carson reported a 50% reduction in infections at 180 days in the coated group (14).

Alterations have also been made to the operating room environment to reduce aerosolized bacteria, including laminar airflow systems and positive pressure devices developed by Brantley Scott (9). To further improve outcomes and the risk of infection, many surgeons have also adopted the "no touch" technique during procedures, as popularized by Eid (15). In this method, the implant, the instruments, and the surgeon's hands never make contact with the patient's skin during the operation. When paired with infection retardant coated IPPs, this "no touch" technique further reduces the rate of infection to 0.46% (15,16).

Despite these advances in technology and technique, infections continue to occur. In a recent multicenter investigation of organisms cultured at the time of IPP salvage or explant, 204 organisms were identified (17). The three most prevalent organisms cultured were *Escherichia coli* (18.3%), followed by coagulase-negative *Staphylococcus* species (15%), and *Candida* species (11.1%).

Biofilm formation

Biofilm formation can be divided into three different phases (*Figure 1*): (I) attachment; (II) maturation; and (III) dispersion [reviewed by Bjarnsholt *et al.* (18)]. In the first phase, planktonic cells attach to a surface and generate a microcolony through clonal growth (19). Once the microcolony has matured, the microbes secrete an insoluble three-dimensional matrix of extrapolymeric substances (EPS, e.g., polysaccharides, proteins, glycolipids, and extracellular DNA) that encase the microbes. Water channels are interspersed throughout the matrix, which permit the distribution of nutrients and oxygen (18). The clonal microbial growth and matrix expansion are highly regulated processes with variable growth patterns, suggesting possible genetic on-off switches. Transcriptome data from *P. aeruginosa* biofilms, however, suggest biofilm development depends more on the microenvironment's nutrient stores, such as glucose, iron and oxygen (20). The final phase of biofilm formation is dispersion, where microbes are released from the biofilm. This can occur either through mobilization of individual bacteria via genetically programmed secretion of enzymes [such as dispersin B (21)] or shearing of biofilm segments allowing sub-colonies to spread.

The trigger of microbial colonies to create biofilms is largely dependent on the environment (e.g., subinhibitory concentrations of antibiotics and the presence of pigments and iron siderophores) (22). Intricate communication systems between adjacent bacteria allow purposeful alterations in colony structure and function, including quorum sensing, chemotactic signaling and plasmid

exchange [reviewed by Ben Jacob *et al.* (23)]. In quorum sensing, cell-to-cell communication synchronizes clonal behavior based on microbial density and nutrient supply. Cell-to-cell communication can also occur through the production of signaling molecules called autoinducers, which manipulate the gene expression of other intra-and interspecies bacteria (24).

Biofilms play an important role in the spread of antimicrobial resistance. The principle mechanism for this is thought to be horizontal transfer of resistance and virulence genes (25). While the mechanisms by which subinhibitory antibiotic concentrations promote the formation of biofilms remain unclear, one potential mechanism in *Pseudomonas aeruginosa* is through induction of the aminoglycoside response regulator (*arr*) gene (26). Increased *arr* expression resulted in activation of cyclic di-GMP signaling cascade and biofilm formation, while *arr* mutants were unable to form biofilms in response to subinhibitory concentrations of tobramycin. Disruption of this communication signaling may provide an avenue for biofilm disruption in the future.

Biofilm therapy

It is well accepted that intravenous antibiotics and/or prolonged courses of oral antibiotics without device removal are ineffective primary therapies for clinically infected IPPs. According to the 2015 recommendations of the International Consultation on Sexual Medicine, attempts should be made to remove all device components in a stable patient with an infected prosthesis and either immediately reimplant another IPP or replace it at a later date. During the explant, steps are taken to remove and disrupt any residual biofilm through parental antibiotics, vigorous antibiotic irrigation of the tissue surrounding the device, and attention to sterile technique. This is not without limitation, however. One-stage and two-stage salvage procedures are associated with an increased risk of post-operative infection, penile fibrosis and penile shortening. Compared to the 1–3% infection rate of initial penile implants, the risk of reinfection increases to 10% for all salvage surgeries and up to 18% among diabetic men (27). Novel treatment strategies are therefore needed to address these biofilms. Various strategies will be discussed in the subsequent chapters based on their mechanism of disruption and their location of action.

Prevention of microbial attachment

A number of different strategies are available that make biologic surfaces inhospitable to microbes. Indeed, the primary strategy to prevent IPP infection is by inhibiting microbial attachment through the use of an anti-infective biomaterial coating. For example, coated implants from Boston Scientific and Coloplast Corporation utilize a hydrophobic layer to create a physical barrier to microbial attachment (28). While many other anti-infective strategies presented in the subsequent paragraphs carry the potential to decrease biofilm formation, their use is speculative and may never be utilized in penile prosthesis material as clinical efficacy testing is lacking.

Microbial surface binding depends on multiple variables that influence adhesion and colonization efficiency, such as the surface shape and chemical properties, environmental conditions, and pathogen specific factors [as reviewed by Campoccia *et al.* (29)]. Non-charged, hydrophilic and hydrophobic surfaces repel microbes floating in protein-rich solutions, such as blood or sera (29). The surfaces also prevent protein attachment, which further impairs bacterial adhesion. Altering the electrical charge of a surface prevents certain proteins in protein-rich solutions from attaching as binding to a hydrophobic or hydrophilic surface requires proteins to undergo a conformational change and disrupts the hydrogen bonds that normally allow hydrophobic segments of proteins to bind to hydrophobic surfaces (30). Thus a change in surface hydrophobicity increases the dependence of electrostatic charge for protein binding. An example of this strategy includes the use of a heparin coating. The application of a heparin coating increases the hydrophobicity of a solid surface and has been used to reduce bacterial adhesion to foley catheter surfaces and intraocular lenses (31-33). While heparin coatings have not been used on penile prostheses, heparin-coated ureteral stents have been tested against common uropathogens including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Following a seven day *in vitro* exposure in a study by Lange *et al.* (34), heparin-coated ureteral stents did not decrease bacterial adherence and exhibited mature biofilm formation. Nevertheless, heparin-coatings may protect penile prostheses from biofilm formation through the interference of *S. epidermidis* adhesins binding to fibronectin (35).

Proteins can also be prevented from surface binding by creating morphologic barriers to their attachment. *In vitro*, smoothness down to the nanometer level, such as those seen on glass surfaces, is associated with reduced Gram-positive and Gram-negative bacterial adhesion (36). In contrast to nanometer scale smoothness, orthopedic implants have

gained from the addition of micro-porous calcium phosphate coating laden with anti-microbial peptides (AMP) (37). These AMPs are short (12–40 amino acid in length), cationic and hydrophobic proteins with broad bactericidal activity (38). A limitation of micro-porous AMP loaded surface is its short-term duration of activity, which may limit its use in penile prostheses. A longer-term alternative to this approach maybe the use of quantum-sized materials called carbon nanotubes (CNT), which exhibit cytotoxicity to bacteria through the creation of oxidative stress and perturbation of the bacterial cell membrane (39). Other antimicrobials fixed to solid surfaces have been tested, including triclosan, chlorhexidine, nitric oxide releasing polymers, coatings release reactive oxygen species, and more recently thermal stress inducing superparamagnetic iron oxide nanoparticles (29). Again, this technology has not yet been utilized with penile prostheses.

Biologic approaches may be utilized to mitigate the clinical burden of biofilm formation on penile prostheses. Similar to other commensal bacteria in our bodies that safeguard against the proliferation of pathologic bacteria, certain bacteria may play a protective role in the adhesion and colonization of other pathogenic bacteria. In a recent analysis of twelve penile prostheses removed due to mechanical failure, Etcheverry-Giadrosich *et al.* (40) found five prostheses colonized with *S. epidermidis* without clinical infection. Biosurfactant produced by these probacteria may inhibit attachment of other virulent strains of bacteria (41,42). It's unclear of the use of probacteria will reach clinical practice as *S. epidermidis* remains a pathogen commonly implicated in the development of IPP infections.

Inhibition of microcolony formation through extracellular polymeric substance disruption

Once microbes attach to a solid surface, biofilms form through microbial proliferation and the microbial production of the scaffolding extracellular matrix. Evolution of these matrices confers a survival advantage as immature biofilms are more antimicrobial susceptible than mature biofilms (43). This resistance with maturation is largely due to the deposition of EPS, which act as diffusion barriers to antimicrobial agents. Furthermore, cell-to-cell communication between microbes aides in resistance development through clonal gene expression changes. Efforts have thus been put forth to disrupt biofilm matrices from maturing and preventing microcolony feedback between microbes. Methods to disrupt these matrices include enzymatic disruption, nutrient deprivation, inhibition of quorum-sensing signals and more recently mechanical disruption through the generation of air bubbles.

One method to destabilize EPS includes enzymatic disruption of the fibrin deposits that act as central structural components of the biofilm. Kwiecinski *et al.* (44) recently demonstrated a reduction in biofilm formation through impaired adhesion and biomass accumulation associated with the application of a tissue plasminogen activator (tPA). The investigators compared tPA-coated versus non-coated coverslips placed in the flanks of mice following a two-hour exposure of the coverslips to staphylokinase-secreting *S. aureus* strains. Three days after implantation, mice were euthanized and the coverslips were examined for biofilm formation. Following explantation, fewer CFUs were attached to the tPA-coated coverslips; however, the difference in bacterial attachment did not differ significantly until tPA-coating was used with antibiotic administration following implantation. Similar findings were found *in vitro* following a 30-minute exposure of tPA-coated polystyrene plate exposure to a bacterial suspension containing. aureus. While the utility of a tpa-coating is limited due to the presence of endogenous plasminogen activator inhibitor (PAI), which neutralizes tPA, an important proof-of-concept was established for the protective role of enzymes in the prevention of biofilm formation.

Mechanical disruption represents another method of biofilm disruption. First developed as a gas-filled micrometer-sized particle encapsulated by a stabilizing shell of either lipids, proteins, or other polymers with the intent of increasing ultrasonography resolution, microbubbles gained additional diagnostic and therapeutic indications in multiple disciplines of medicine. Microbubble-assisted ultrasonography now allows targeted drug delivery (45,46), delineates anatomy intraoperatively (47), facilitates gene therapy through alterations in cell membrane permeability (48), and creates the cavitations necessary for mechanical disruption of biologic fluid and tissue membrane interfaces (*Figure 2*) (49). Li *et al.* (50) recently compared ultrasound targeted microbubble destruction (UTMD) to the combined effect of UTMD + cationic antimicrobial peptide, Human β-3-defensin 3 (HBD-3), on *S. epidermidis* and *S. aureus* biofilm coated titanium plates implanted into a mouse model. Three days after treatment with either ultrasound (US) alone, UTMD or UTMD+HBD-3 at various doses, the number of viable colony forming units (CFU) and biofilm densities were compared. The number of viable CFUs per square centimeter significantly decreased in biofilms treated

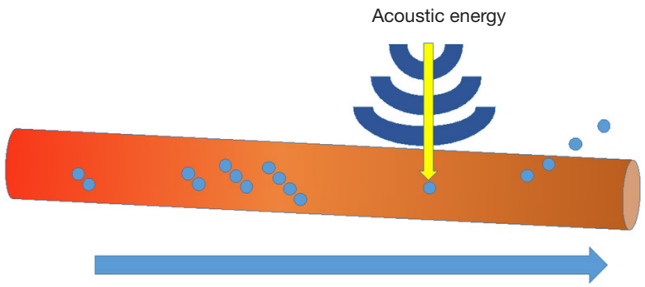

Figure 2 Intravenous microbubbles pass ultrasound waves inducing microbubble cavitation and penetration of vasculature to allow penetration into extravascular space.

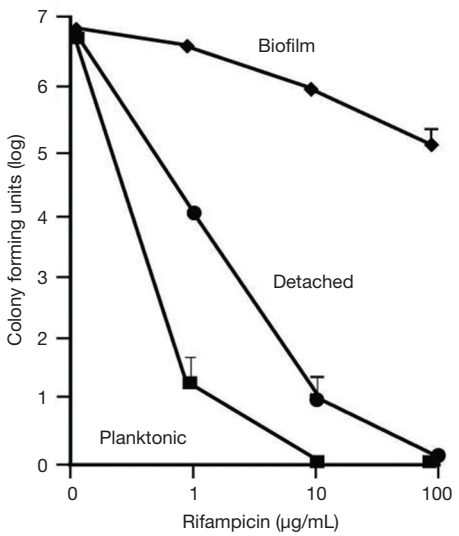

Figure 3 Susceptibility of biofilm, detached bacteria, and planktonic bacteria to Rifampicin. Adapted from Boles and Horswill (53) used under CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/).

with HBD-3 + US and HBD-3 + UTMD, with the lowest CFUs observed in the cohort of mice treated with HBD-3 and UTMD. The authors showed enhanced antimicrobial activity of HBD-3 with the addition of UTMD. However, the degree of the air bubble's mechanical insult effect depends on biofilm age and biofilm thickness and additional studies need to be performed to determine whether microbubbles and antimicrobial peptides will play a role in preventing and treating biofilms attached to IPPs.

Biofilm dispersion-inducing agents

Environmental cues and stress states (such as nutrient deprivation, excessive waste product accumulation, nitrogen and oxygen deprivation) induce biofilm dispersion and release of microbes (43,51). Therefore, strategies to coax biofilm-coated microbes to shed their protective coating represent another method for biofilm control. Dispersion-based strategies have utilized genetic regulation of various intracellular signal transducers and activation of endogenous EPS enzymes integral to the dispersion of established biofilms. In an analysis of genes necessary for the dispersion of *Pseudomonas putida* using a transposon screen, Gjermansen *et al.* (52) identified the LapG protein as a member of outer membrane transglutaminases-like cysteine proteinase family that modify bacterial surface structures. This family of proteins is critical to biofilm formation as *P. putida* mutants lacking the lapD gene are not able to form biofilm. In a subsequent study by Gjermansen *et al.* (51), LapG and LapA protein function were modulated by altering intracellular c-di-GMP levels to determine the two protein's impact on biofilm formation and eventual dispersion. The authors found increased LapG proteinase activity under lowered c-di-GMP levels resulted in increased LapA protein digestion. Moreover, loss of LapA protein, which normally functions as a surface adhesin protein and biofilm matrix component, led to dispersal of *P. putida*. Reduction of c-di-GMP represents and LapA protein activity therefore represents mechanisms to promote dispersion; however, this mechanism is *Psuedomonas* specific.

Unlike *Pseudomonas*, active quorum-sensing in *S. aureus* prevents biofilm formation (53). Quorum-sensing in *S. aureus* is controlled by the accessory gene regulator (*arg*) locus. The *agr* locus of *S. aureus* constitutes a system of transcriptional regulators that control virulence-associated genes and communication molecules that are both produced and self-sensed, called autoinducing peptides (AIP) (54). The *agr* system activates with glucose depletion and the introduction of autoinducing peptides (AIP). Boles and Horswill (53) demonstrated that the administration of exogenous AIP to wild-type strains of *S. aureus* resulted in biofilm sloughing using a confocal laser scanning microscope. More importantly, S. *aureus* that detached from their biofilm regained susceptibility to antibiotic exposure (*Figure 3*). Thus, disruption of *arg* gene function of *S. aureus*

represents another avenue to induce biofilm dispersion.

Conclusions

Biofilms are three-dimensional communities of microbes that can attach to an implant surface. Biofilms confer antimicrobial resistance enhancing microbial survival in hostile environments, damage surrounding tissues, and trigger inflammation. Unfortunately, biofilms can form on IPPs and represent a feared complication of penile prosthesis surgery. Despite the progress made in aseptic technique and device coating, the infection rates remain approximately 1–3%. Current management of IPP infections often necessitates device removal for successful eradication of the biofilm. However, several promising anti-biofilm strategies are under development that may someday circumvent the need for device explantation. Efficient and effective methods are urgently needed beyond those available to prevent and treat biofilm formation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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