Review Article

A scoping review of penile implant biofilms—what do we know and what remains unknown?

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Background: Penile prosthesis (PP) is a gold standard for treatment of erectile dysfunction given its reliability and efficacy. Infection remains the most feared complication of prosthetic surgery, which usually results in device removal, and places a significant economic burden on the healthcare system. While biofilms have shown to support the persistence of microorganisms, the degree by which this matrix is truly pathogenic remains unknown given its high prevalence even in asymptomatic patients. We aim to review and summarize the current literature pertaining to biofilm formation in the setting of PP surgeries in clinically infected and non-infected cases.

Methods: Searches were performed in the MEDLINE online database through PubMed using a combination of keywords "penile prosthetic" OR "penile prosthesis" OR "penile implant" AND "biofilm" OR "revision" OR "removal" OR "infection" OR "explant". Eleven articles met inclusion criteria. There were only three studies that explicitly listed the number of biofilms identified in their cohort, but we also included eight articles that mentioned swabbing and culturing of any bacterial biofilm during revision procedures for both clinically infected and non-infected implants.

Results: Infected PP yielded a 11–100% rate of biofilm presence, while non-infected PP yielded a 3–70% rate of biofilm presence. Time to reoperation from initial PP placement were also largely variable, ranging from 2 weeks to over 2 years. Coagulase-negative staphylococcus (i.e., *Staphylococcus epidermidis*) were the most commonly reported organisms among non-infected implants, however, newer studies have identified a change towards more virulent organisms.

Conclusions: Since the advent of PP surgery, diabetes control, revision washout protocols and antibiotic-impregnated devices have led to an overall decrease in biofilm formation and infectious complications. There is an overall paradigm shift in microbial profiles with more virulent organisms, such as *Escherichia coli*, *Pseudomonas aeruginosa*, Enterococcus species, and even fungal species beginning to replace the more common coagulase-negative staphylococcal species, especially in clinically infected implants. Additional studies are necessary to define the significance of bacterial presence in biofilms using impactful technologies such as next-generation sequencing. Currently, preliminary and experimental biofilm-control strategies are also underway to further address this clinical issue.

Keywords: Penile prosthesis (PP); biofilm; infection; antibiotic

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Introduction

Due to its long-term durability and high rates of patient and partner satisfaction, penile prosthesis (PP) implantation is now regarded as a gold standard treatment for medically refractory erectile dysfunction (ED) (1,2). According to the American Urological Association guidelines, PP can be considered as a first-line treatment option for ED, which differs from the previously recommended stepwise approach (3). Recent reviews have suggested that PP implantations may not only be the most effective treatment for ED, but also the most cost effective compared to other medical therapies in specific populations, such as those after ischemic priapism (4-6). With the growing body of literature surrounding the efficacy of PP for ED, device failure rates and surgical complications have also been well established. Of these, infection remains the most concerning sequelae, often necessitating device removal and subsequent revision surgery with suboptimal outcomes (7).

Device infections are thought to be caused by the introduction of microorganisms via incisions at the time of surgery or via hematogenous spread. Typically, the host defense mechanisms and prophylactic antibiotics kill the bacteria; however, in the setting of medical device implantation into a surgical wound, the implant is rapidly coated with serum proteins and ultimately the body deems it as a foreign body and coats it with a conditioning layer of fibrous capsule, which can alter the surface characteristics of the inanimate object (8). This serum-coated surface is ideal for bacterial adherence and subsequent biofilm formation (*Figure 1*). Bacterial biofilms are communities of adherent bacteria protected against the body's immune system and antibiotics by a protein-containing polysaccharide matrix. During this process, the cells undergo phenotypic changes that render them less metabolically active and, therefore, more drug resistant (9). The risk of device infection is further increased after revision surgery due to weakened host-resistance factors, impaired wound healing related to scar formation and, most importantly, decreased antibiotic penetration secondary to bacterial biofilm formation (10).

Bacterial biofilms are problematic to the prosthetic surgeon and catastrophic for the patient as they are extremely difficult to prevent or treat. Within the urologic field, biofilms can cause complications with simple devices such as urethral catheters or indwelling ureteral stents, as well as PP implants. An understanding of these biofilms and the microbes they harbor is essential to understanding the pathophysiology of device infection and malfunction. Herein, we aim to provide the readership with a scoping review of the current literature pertaining to biofilm formation in the setting of PP surgeries. We present the following article in accordance with the PRISMA-ScR reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-195/rc).

Methods

A literature review of articles indexed in the MEDLINE online database was performed through PubMed from January 2022 to February 2022. Keyword searches including a combination of the terms "penile prosthetic" OR "penile prosthesis" OR "penile implant" AND "biofilm" OR "revision" OR "removal" OR "infection" OR "explant" were utilized to identify appropriate articles to include in our review in accordance with the PRISMA Extension for Scoping Reviews protocol (11). Only original articles that were peer-reviewed and published in English were included. There was no limit placed on publication year. Article types including editorial comments, review articles or systematic reviews and meta-analysis were excluded. Articles spanned from 1953 to 2022. Titles, abstracts, and full texts were reviewed for inclusion based on appropriateness by three authors (JYL, CEC, MJD) independently. Articles were only included if they specifically identified or cultured biofilm during PP revision surgeries. Variables including presence of biofilm, microbial data (number of isolates, number of species, organism type), time to reoperation, culture sensitivities and administered antibiotics were abstracted. Upon identifying and screening the 160 eligible articles, a total of 11 articles that met inclusion criteria were found (*Figure 2*). We included an early case report that first described and identified biofilm in two patients with infected PP implants. We qualitatively analyzed and summarized the data from these articles and descriptively presented them in *Table 1*.

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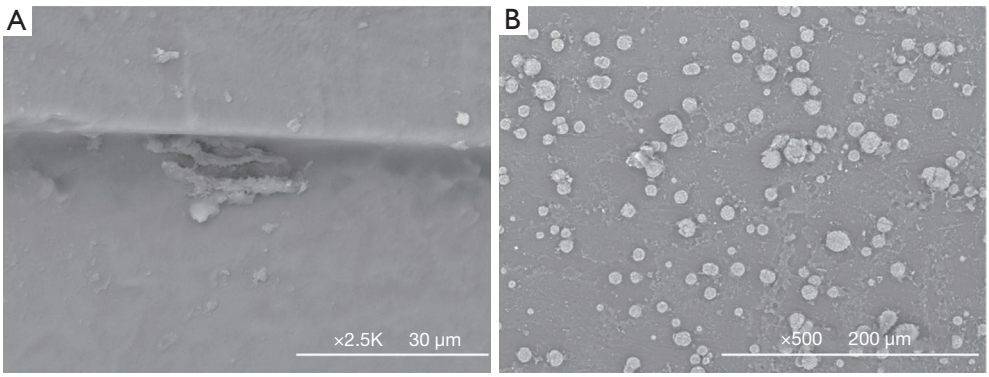

Figure 1 Implant surfaces from devices explanted for mechanical malfunction, preserved with formalin, dried, gold sputter-coated and visualized by scanning electron microscope, (A) pump, (B) cylinder. (A) Surface features and apparent bacterial biofilms sequestered in an implant crevice; surface irregularities are favored for bacterial attachment. (B) Surface texture and extensive cellular colonization among biological debris, morphology is consistent with white cells.

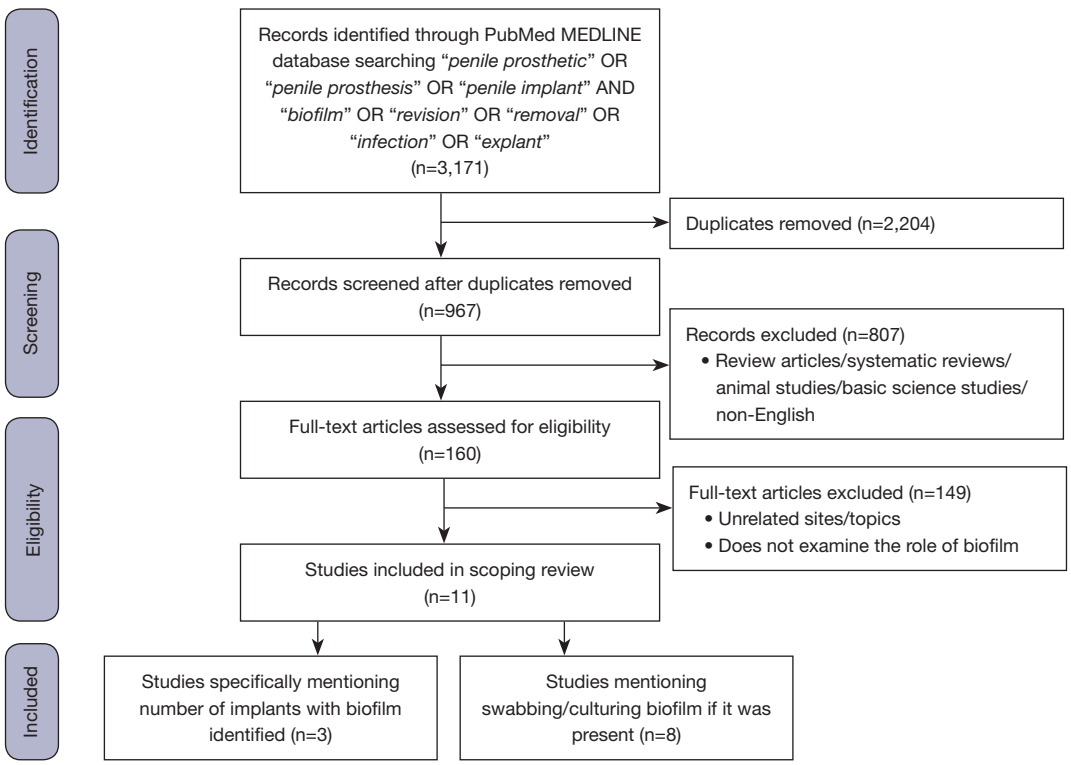

Figure 2 PRISMA-ScR flowchart of database search.

Results

While there were only three studies that explicitly listed the number of biofilms identified in their cohort, we also included eight others that mentioned the swabbing and culturing of any bacterial biofilm during revision procedures for both clinically infected and non-infected implants. These results are summarized in *Table 1*.

The first study describing biofilms on PP was published by Nickel *et al.* in 1986 whereby two patients with clinically infected PP harbored rod and coccoid shaped bacterial

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Table 1 Presence of biofilm on penile prosthesis implants during revision surgery

First author, year	Percentage of biofilm present	Microbial data			Time to reoperation, median (range)	Culture sensitivities	Perioperative antibiotics
		Number of isolates	Number of species	Organism type			
Chung, 2022*	48/83 (56%) on next-generation sequencing; 24/83 (29%) on standard culture	–	21	Infected: *P. aeruginosa* (50%); Erosion: *S. epidermidis* (75%); Mechanical malfunction: *E. coli* (72%)	28 months (interquartile range 43.5 months)	Vancomycin + gentamicin with broadest coverage	–
Gross, 2020*	71%	–	–	Gram-positive bacteria (44%), Gram-negative bacteria (25%)	2 months (2–81 months); mean 5.4 months	–	–
Gross, 2019*	26/26 (100%) infected implants (fungal)	26	5	Candida sp. (97%), *C. albicans* (62%)	4.8 months (12–120 months)	–	In addition to standard perioperative antibiotics, no patients received antifungals at initial implantation, 15% received antifungals before explant, 31% received antifungals during explant
Jani, 2018*	130/236 (55%)	127	27	Staphylococcal sp. (77%), *S. epidermidis* (43%)	Mean 56 months (standard deviation 51 months)	All isolates sensitive to tetracycline/ rifampin	–
Gross, 2017*	153/227 (67%) infected implants	204	35	*E. coli* (18%), Coagulase-negative Staphylococcal sp. (15%), Candida sp. (11%)	1.5 months (0.5–81 months); mean 4.8 months	Vancomycin + gentamicin OR vancomycin + aztreonam (86% efficacy)	Implantation: 56% vancomycin/gentamicin, 22% ancef/gentamicin; Salvage/explant: 50% vancomycin/gentamicin, 15% ancef/gentamicin
Ciftci, 2016	2/71 (3%) non-infected implants; 2/18 (11%) positive culture	5	21	*S. epidermidis* (57%), 2/2 biofilms cultured *S. epidermidis*	41 months (8–82 months)	–	–
Kava, 2011*	5/51 (10%)	7	6	*S. epidermidis* (29%)	9.6 months (6–138 months)	–	–
Henry, 2008*	97/148 (66%) non-infected implants	124	20	Staphylococcal sp. (87%), *S. epidermidis* (44%)	Mean 47.9 months (range 1–190 months)	–	–
Silverstein, 2006	7/10 (70%) non-infected implants; 7/8 (88%) positive culture	–	–	Gram-positive cocci (80%), Gram-negative rods (70%), Yeast (60%)	>2 years	–	–
Henry, 2004*	54/77 (70%) non-infected implants	64	15	Staphylococcal sp. (81%), *S. epidermidis* (39%)	Mean 53 months (range 2–190 months)	All Staphylococcal sp. isolates sensitive to tetracycline/ rifampin	–
Nickel, 1986	2/2 (100%) infected implants	–	–	Coccoid bacterial cells (100%), *P. aeruginosa* (50%)	1 month; 2 years	–	Cefalexin; trimethoprim-sulfamethoxazole

*, Studies did not explicitly mention the number of biofilms identified, but noted that bacterial biofilm was swabbed and cultured if observed during salvage procedure.

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cells (12). These patients were successfully treated with oral antibiotics. The next study by Silverstein *et al.* found a 70% rate of biofilm formation among non-infected, non-antibiotic coated implants, 88% of which did have positive cultures (13). Most recently in 2016, Ciftci *et al.* identified biofilm in 11% of implants removed for non-infectious reasons, all of which grew *Staphylococcus epidermidis* (14).

Next, we also noted that for non-infected implants or implants removed secondary to mechanical malfunction, the most common reported organisms were coagulase-negative staphylococcus (i.e., *S. epidermidis*), which ranged from 15–81% in our cohort. Conversely, implants removed for infection harbored other organisms such as *P. aeruginosa* in 50% of one reported cohort or *E. coli* in 18% of another cohort.

The percentage of biofilm presence were based on whether the PP were clinically infected or not. When PP were infected, the rate of biofilm presence ranged from 11–100%, while biofilm presence ranged from 3–70% in non-infected PP. Time to reoperation from initial PP placement were also largely variable, ranging from 2 weeks to over 2 years.

Discussion

What is biofilm?

Historically, biofilm is defined as "a structured consortium of bacteria encased in a self-producing matrix that exhibits a unique pattern of gene expression and growth" and is almost always associated with a surface for attachment (15-17). Its structure can be divided into three layers—a deep, linking layer abutting the adherent surface, a compact base layer of bacteria, and a superficial surface film on which free-floating bacteria can arise and spread (18).

Biofilm formation can be distilled down to four phases—attachment, aggregation, maturation and detachment (19). The first stage is arguably the most important step, and involves foundational forces and biological proteins from planktonic bacteria that establish interactions to adhere to the inanimate substratum (15,18). The second stage involves accumulation, growth and development of cell layers on the surface. During the third maturation phase, the insoluble three-dimensional matrix or extracellular polymeric substance (EPS) is formed. This "film" encases the microbes and serves as a channel for bulk fluids to flow and permits the distribution of chemical signals and nutrients (20). Lastly, as the colonies grow, quorum sensing occurs triggering expression of cleavage enzymes that subsequently release bacteria from the colonies resulting in the last step, detachment and dispersion (21). These bacteria are now free to seed other locations within the host and begin the cycle anew (22,23).

The challenges of biofilm

Biofilm can be particularly problematic to prosthetic surgeons and patients as they are not only resistant to most traditional treatments but are also difficult to prevent. Most antibiotic strategies, such as identifying the minimum inhibitory concentration of an antibiotic to determine the appropriate amount of drug for a specific strain of bacteria, are designed for planktonic bacteria and may be insufficient for adherent bacteria, sometimes by several orders of magnitude (24). While current antibiotics were designed to eradicate planktonic bacteria, biofilm colonies are not so easily studied as they are difficult to reproduce by standard methods (16,22). These infections also tend to resist innate and adaptive immune responses as well as antimicrobial agents due to their thick extracellular matrix that serves as a barrier to impede the penetration of antibiotics (25). Moreover, antibiotics that do reach the microbe biomass layer may be rendered less effective due to their reduced metabolism and sub-therapeutic concentrations. Finally, biofilms are slow growing to the point of dormancy, and these "persister cells" have the ability to remain viable even after treatment with very high doses of antibiotics (26).

With regards to PP implants, the formation of a fibrous capsule represents another hurdle for antibiotic treatment and penetration of infected implants. These capsules are typically avascular, which further results in reduced antibiotic delivery to the intended area of treatment (27). With reduced drug delivery, there is decreased distribution of chemotactic signals, e.g., cytokines that are necessary to induce an inflammatory response or stimulate neutrophils to reach microbes deep within the biofilm colonies (15).

Biofilms may possibly play a role in the spread of antimicrobial resistance through the horizontal transfer of resistance and virulence genes when in close proximity within the extracellular biofilm matrix (28). Exposure to subtherapeutic concentrations of antibiotics allows for selection pressures and the potential for development of resistant or virulent strains of bacteria. Together, the challenges in treating biofilms associated with prosthetic-associated infections emphasize the importance of prosthesis removal in most cases.

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Biofilms in penile prostheses

Biofilm development is widely accepted as a pathologic step in PP infections, and their tolerance or resistance to traditional antimicrobial regimens heightens their clinical importance. Prosthetic surgeons have attempted to use standard culture results to tailor antibiotic therapy for revision patients. Nonetheless, multi-institutional data evaluating clinically infected PP explants have documented non-specific or even no growth cultures in up to 33% of cases (29). This may be secondary to flaws in culture collection techniques, the administration of antibiotics prior to culture collection, or the challenges in growing and identifying all biofilm-associated microbes (8).

With the advent of infection-retardant coatings and revision washout protocols, current literature documents a decrease in infection rates from 2–4% to less than 2% in primary implants, and from 7–18% to 2–3% in revision cases (10,30-35). Moreover, recent systematic reviews report a change in the microbial composition in clinically uninfected and infected PP over time (29). The abundance of coagulase-negative staphylococcal species, most commonly *S. epidermidis*, have shown a decreased proportion in cultures for explanted PP. Other species such as *E. coli*, *P. aeruginosa*, Enterococcus species, and even fungi that form biofilms have been on the rise (29,36).

Table 1 summarizes the review of the presence of biofilm identified on PP revision surgery for both clinically infected and non-infected implants. While there were only three studies that explicitly listed the number of biofilms identified in their cohort, we also included several others that mentioned swabbing and culturing of any bacterial biofilm during revision procedures. In 1986, Nickel *et al.* described one of the first instances of biofilm presence in two patients with clinically infected PP, both of which harbored rod-shaped and coccoid bacterial cells (12). Subsequently in 2006, Silverstein *et al.* described the presence of bacteria on laser microscopy among eight of ten non-antibiotic coated-PP explanted for mechanical function, seven of which had biofilm (13). Ciftci *et al.* also specifically identified biofilm in two of 18 non-infected implants who had a positive culture; both of these biofilms grew *S. epidermidis* (14). Most recently, Chung *et al.* also identified biofilm on both standard culture and next-generation sequencing (NGS) in 24 and 48 of 83 samples, respectively (36). Interestingly, this pilot study was the first to assess the utility of NGS in the detection of biofilm and was not only able to detect microbes better than traditional culture, but also detected different microbial profiles for PP explanted for different surgical indications. This may help guide the selection of peri-operative antibiotics and PP-coated antibiotics or hydrophilic dips for individualized scenarios.

Based on historic trends, in revision cases performed for clinically uninfected cases, most cultures from explanted PP are positive for *S. epidermidis*, a part of common skin flora. Even in the setting of infected PP, the reported presentations are typically with lower toxicity and are confined to the implant space. These bacteria are likely introduced during primary implantation and once they form their mucinous biofilm, they appear able to live in the PP environment without always causing clinical signs of infection (10,27). During revision or salvage procedures, the disruption of pre-existing biofilms and dissemination of these bacteria are thought to contribute to the higher infection rates (37).

In recent articles assessing antibiotic-coated implants, the prevalence of Staphylococcal cultures seems to have decreased, with a slow rise in the incidence of more toxic organisms such as *E. coli*, *P. aeruginosa*, Enterococcus species, and even fungal species, such as *C. albicans*. The recent multi-centered study by Gross *et al.* assessing cultures in 227 infected implants undergoing revisions found that *E. coli* was the most common isolate (18%), coagulase-negative staphylococcus was the second (15%), and Candida species isolates were the third most common (11%) (29,38). Even more recently, a study using NGS found that *P. aeruginosa* and *E. coli* were the most frequent and abundant organisms encountered in their cohort of infected and mechanically malfunctioned patients, respectively (36). Some reports have also demonstrated a discrepancy in the culture data between the first revision surgery for non-infectious reasons when compared to the second revision for infectious etiologies (14). Of 202 revision surgeries for infection reported by Chandrapal *et al.*, they found that only 22% of implants grew the same organisms at explantation for infection when compared to their original swabs at first revision (39).

Current applications to reduce biofilm attachment

Advances in PP designs with the use of infection-retardant coatings have also led to significant decreases in overall PP infection rates (40). Boston Scientific (Marlborough, MA) introduced the InhibiZone technology into the AMS 700 inflatable PP in 2001, which contains minocycline

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and rifampin (41). Devices were impregnated with this combination due to the low incidence of allergies and the efficacy of these antibiotics against Gram positive and negative bacteria commonly seen in PP infections (41). The Coloplast (Minneapolis, MN) Titan inflatable PP comes with a hydrophilic coating in 2002, known as polyvinylpyrrolidone, which absorbs an antibiotic when dipped into an aqueous solution, giving prosthetic surgeons more flexibility when tailoring their antibiotic of choice (42,43). While the ideal antibiotic solution and "dipping time" have yet to be described, a combination of vancomycin and gentamicin mixed in normal saline solution is typically the antibiotics of choice unless clinically contraindicated due to its broad coverage against most Gram positive and negative microbes. Due to its convenience and efficacy, some authors have also studied the utility of Irrisept (Irrimax Corporation, Lawrenceville, GA), a low-concentration 0.05% chlorhexidine gluconate solution that has broad spectrum antibacterial, antifungal, and antiviral properties as a dipping solution (44). They found satisfactory coating results on Coloplast Titan PP when compared to saline soaked controls. Furthermore, they found no difference in coating adherence between soaking times of 1, 15, 30 and 60 minutes. The introduction of antibiotic-coated PP has also been shown to improve infection-free survival in diabetic cohorts (45). A systematic review and meta-analysis of 14 clinical case studies found the rates of infectious complications to be significantly lower in the cohort with antibiotic coated prostheses at 0.89% when compared to those without (2.32%; $P<0.01$) (46). A recent study performed by Jani *et al.* also found higher rates of culture positive isolates in uncoated PP regardless of whether explant surgery was performed for infectious or non-infectious etiologies (47). Overall, the utility of antibiotic coatings confers significant advantages in preventing postoperative device infections (48,49).

The use of antibiotic washout during revision surgery is also a critical step that has been shown to significantly reduce infection rates. Mulcahy *et al.* first revolutionized the management of infected PP by assessing the feasibility of immediate replacement of inflatable PP at the time of revision surgery after a seven-step antibiotic irrigation protocol (50). Prior to the introduction of the salvage technique, treatment of PP infection involved the removal of all prosthetic components along with copious antibiotic irrigation to the PP site (51). This often resulted in fibrosis and scarring of the corpora cavernosa, complicating subsequent reimplantation in the future. Since the development of the Mulcahy protocol in 1996, other groups have demonstrated promising results with the use of the immediate salvage technique and also modified their techniques with a delayed or malleable salvage method with other antibiotic irrigation solutions (52-56). For example, cohorts from Wilson and Henry both reported a reduction of infection rate from 10% to 3% in the cohort who underwent antiseptic washout after revision surgery (27,33). Importantly, while antibiotic coatings on PP have demonstrated desirable outcomes in primary surgeries, its effects on revision cases are less pronounced, and studies have noted decreased rates of infection in revision surgeries only if adjunctive revision washout was performed (33,57). This indicates that while antibiotic coatings can prevent infections secondary to planktonic bacteria during initial implantations, once biofilms are established, a more rigorous irrigation and lavage is necessary to eliminate latent microbes and disrupt biofilms in previous implant spaces (10). Hence, revision washout is recommended even in patients who undergo revision for non-infectious indications (27). A report by Abouassaly *et al.* also commented that revision washouts should be aggressive, with the use of copious amounts of one type of antimicrobial solution rather than smaller amounts of several antibiotics (58). Occasionally, mechanical debridement of biofilm in the implant space may also be necessary.

Patients with prior PP who are undergoing revision surgeries are also considered high risk for infection, likely for reasons related to biofilm formation as mentioned previously. Traditionally, revision surgeries have a 10–13% rate of infection, a significantly higher percentage when compared to primary cases at <3% (32,33). Another study demonstrated that risk of device infection strongly correlated with an increased number of implantations with 6.8% risk for the primary implantation compared to 100% by the fifth implantation (59). Finally, the consequence of device infection is multifactorial; hence, careful patient selection, paired with the advent of recent technological innovations is essential to ameliorate the risk of this complication.

Future of biofilm prevention and treatment

While there are many novel possibilities for the prevention and treatment of bacterial biofilms, the majority of these methods are still in the experimental phase and are still being studied *in vitro*. Given the surgical volume in orthopedics and neurosurgery, most innovative

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biomaterial strategies are focused on these implants, but the advancements can be translated to the urologic prosthetic realm (9). The primary strategy to prevent biofilm formation and subsequent device infections is to prevent bacterial attachment altogether. Surface modification or impregnated antibiotic are methods that can render biologic surfaces inhospitable to microbes. Both the Boston Scientific and Coloplast inflatable PP are coated implants, but only the Coloplast malleable PP is coated with a hydrophilic layer to create a physical barrier to prevent microbial attachment (23). A new inflatable and malleable PP from Rigicon (Ronkonkoma, NY) also supports a hydrophilic layer (60). Changes in hydrophobicity as a result of altering the electrical charges of a surface can also prevent certain proteins from binding to solid surfaces. For example, the application of heparin coating has been used on intraocular lenses and urethral catheters to reduce bacterial adhesion (61-63). The addition of morphologic barriers such as antimicrobial peptides have also been utilized in the orthopedic field (64-68). However, these peptides have shorter duration of action which may pose a limitation for its use in PP. Other antimicrobials that have been tested for prosthetic coating include chlorhexidine, nitric oxide and triclosan, but have not been used in PP (69). Also, biologic approaches such as the use of commensal bacteria to prevent the colonization of pathogenic bacteria may play a protective role in the adhesion and proliferation of pathologic bacteria. The use of biosurfactant produced by these probacteria to inhibit attachment of other virulent strains of bacteria in clinical practice is still unclear (70,71).

Aside from targeting adhesion, the first phase of biofilm formation, studies have attempted to inhibit microcolony formation by disrupting the EPS. The formation of EPS allows for cell-to-cell communication between microbes that aid in the development of resistance through clonal gene expression changes and can also act as a diffusion barrier for antibiotics (23). One method to destabilize the EPS include enzymatic disruption of fibrin deposits that act as the central structural unit of biofilms with the use of tissue plasminogen activator. Mechanical disruption using microbubble-based, contrast enhanced, ultrasound imaging creates cavitations that disrupt the biologic fluid and tissue membrane interfaces of biofilm (72). It can delineate anatomy intraoperatively, allow for targeted drug delivery and facilitate gene therapy through alterations in cell membrane permeability, as seen in hepatobiliary anatomy (73-77). In 2015, an *in vivo* study by Li *et al.* evaluated the effects of ultrasound-targeted microbubble destruction in combination with a cationic antimicrobial peptide, human β-defensin 3 on antibiotic-resistant Staphylococcus biofilms (78). Their findings suggest that the combination of ultrasound use significantly decreased the biofilm densities, percentage of live cells, and viable counts of tested Staphylococcus colony forming units. The degree of mechanical insult induced by acoustic rupture of these microbubbles depends largely on biofilm age and thickness. Future work is necessary to determine if this modality will be a safe and efficacious method in preventing or treating PP biofilms.

Experimental studies evaluating dispersion-inducing agents that coax microbes to shed their protective biofilm coating may be an important proof-of-concept that can aid in biofilm control. Studies in *S. aureus* species have shown that active quorum-sensing prevents the formation of biofilm (79). The disruption of the accessory gene regulator (agr) gene function, which mediates the quorum-sensing mechanism, may theoretically represent a method to induce biofilm dispersion (79,80). In *Pseudomonas* species, alterations in genetic regulation of intracellular signal transducers e.g., Lipopolysaccharide assembly protein A (LapA) proteins, and activation of EPS enzymes e.g., LapG proteinase, represents mechanisms to promote dispersion of established biofilms as well (81,82).

Recently, emerging technologies have allowed for more sensitive and superior testing, one of which is the advancement of rapid molecular sequencing. Our group recently performed a study assessing the utility of a novel technology, NGS, for the identification of microorganism profiles on explanted biofilms (36). We found that NGS was able to detect microbes more abundantly and frequently when compared to standard culture and that the microbial profiles differed based on etiologies for revision surgery, including infection, erosion, or mechanical malfunction. We also found that NGS tended to detect a polymicrobial profile, while culture results were only monomicrobial. Although the significance of the polymicrobial findings detected by NGS have yet to be ascertained, these findings may guide surgeons in the selection of perioperative antibiotics and hydrophilic antibiotic dips in individualized clinical scenarios for the treatment of biofilms (36,83).

Limitations

There are some limitations to our scoping review process. While it entails a different screening criteria or process than a systematic review, it is a broader and less refined search.

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It also requires multiple search strategies and increases the emphasis for hand searching within individual articles. Hence, it requires a larger team for screening larger volumes of literature which may lead to inconsistencies in interpreting and conducting these reviews. There is also a possibility that we may have missed some relevant studies due to database selection or inclusion of only articles published in English. Depth of analysis may be limited by time constraints as well to review all articles. Lastly, the lack of critical appraisal of included studies is also a limitation. It cannot be used to endorse guideline recommendations as it did not assess the quality of included studies and is also limited to identifying gaps in the literature related to low quality research.

Conclusions

PP remains the gold standard for treatment of ED given its reliability and efficacy. Infection remains the most feared complication of prosthetic surgery, which usually results in device removal. While biofilms are believed to be the culprit, the degree to which this bacterial matrix is truly pathogenic remains unknown—especially given its high prevalence even in asymptomatic patients. What has been noticed is that in the era of antibiotic-coated implants, less common, but more virulent organisms are beginning to replace the more common Staphylococcal species in clinically infected implants. These patients also present with more toxic, systemic infections and ultimately require device removal altogether for source control. While revision washout protocols and antibiotic-coated implants have decreased overall infection rates, testing of preliminary and experimental biofilm-control strategies is necessary to further address this clinical issue. Moreover, additional studies including a prospective, randomized controlled trial is currently underway to define the significance of bacterial presence in biofilms using innovative technology such as NGS.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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