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REVIEW

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Current treatments for biofilm-associated periprosthetic joint infection and new potential strategies

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Abstract

Periprosthetic joint infection (PJI) remains a devastating complication after total joint arthroplasty. Bacteria involved in these infections are notorious for adhering to foreign implanted surfaces and generating a biofilm matrix. These biofilms protect the bacteria from antibiotic treatment and the immune system making eradication difficult. Current treatment strategies including debridement, antibiotics, and implant retention, and one- and two-stage revisions still present a relatively high overall failure rate. One of the main shortcomings that has been associated with this high failure rate is the lack of a robust approach to treating bacterial biofilm. Therefore, in this review, we will highlight new strategies that have the potential to combat PJI by targeting biofilm integrity, therefore giving antibiotics and the immune system access to the internal network of the biofilm structure. This combination antibiofilm/antibiotic therapy may be a new strategy for PJI treatment while promoting implant retention.

KEYWORDS

antibiofilm treatments, biofilm, infection, periprosthetic joint infection

1 | INTRODUCTION

With increases in the population and life expectancy, more foreign objects are implanted into patients every year.[1] These implants include orthopedic hardware (arthroplasties, plates, rods, screws), pacemakers, stents, and so forth.[2,3] While these devices can be lifesaving or improve a patient's quality of life, complications including infection are still a commonplace. While infections are quite rare, the burden on the individual's well-being and the economic burden is high.[4]

In orthopedics, total joint arthroplasty has been proven to have excellent survivorship while increasing function and decreasing pain for millions of patients every year in the United States.[5–7] While a majority of patients do not experience any adverse events, 0.5%–1.4% of primary arthroplasty patients[8,9] and 18%–30% of revision arthroplasty patients[10,11] develop a devastating complication of periprosthetic joint infection (PJI). PJI cases are estimated to be over 70,000 cases per year costing over $1.6 billion in the United States[4] with estimates increasing between 68% and 176% for revision hip and 72%–170% for revision knees by 2030.[12] Furthermore, PJI has a 5-year mortality rate of 26%, similar to many common cancers, making it a major healthcare challenge.[13]

2 | PJI-ASSOCIATED BIOFILMS

Bacteria are present in two states—free-floating easily cultured planktonic or biofilm matrix-associated. Bacteria in a biofilm matrix are present at various metabolic states making cultures difficult to obtain and

therefore treat.[14] Bacterial biofilm is notorious for attaching to foreign material where gram-positive *Staphylococcus epidermidis* (*S. epidermidis*), *Staphylococcus aureus* (*S. aureus*), and gram-negative *Pseudomonas aeruginosa* (*P. aeruginosa*) account for 75% of biofilms on medical devices including catheters, shunts, pacemakers, and other orthopedic devices.[15–17] *S. aureus* has been reported as one of the most common bacterial strains associated with knee and hip PJI, accounting for upwards of 38% of joint infections (refer to this review for an extensive list of bacteria associated with PJI).[8] The presence of a foreign body can decrease the inoculation dose required for infection by 100,000-fold in the case of *S. aureus*.[18] Bacterial biofilms also act as protective barriers from antibiotics, increasing their resistance 1000-fold in the case of *P. aeruginosa*,[19] and evading host defense mechanisms. Adherent bacterial cells forming biofilm are encapsulated in a matrix composed of extracellular polymeric substances (EPS) including polysaccharides, proteins, glycoproteins, glycolipids, and extracellular DNA (eDNA).[20] Additionally, bacteria can communicate with other cells within a population via gene regulation to promote phenotypes most beneficial to their community (quorum sensing).[21]

In the case of *S. aureus*, bacterial reservoirs that evade the host immune system and antibiotics are not only found on implant surfaces but can also be found deep within the bone via invasion of the osteocyte lacuno-canalicular network, can persist intracellularly in bone cells, and in staphylococcus abscess communities (refer to these references for additional reading on these topics[22–27]). Although these reservoirs are important in the underlying pathogenesis of infection and treatment failure, this review will focus on bacteria present in biofilms on implants and strategies to combat this, with implant retention in mind. Of note, in addition to the use of a high concentration of local antibiotics (intra-osseous or intra-articular), some of the types of technology mentioned in this review have also been shown to prevent and treat established bacterial reservoirs in addition to having antibiofilm effects and therefore have the potential to target multiple bacterial communities.[28–32]

3 | PJI MANAGEMENT

PJI are commonly categorized into acute or chronic infections based on the likelihood of success with debridement, antibiotics, and implant retention (DAIR) where higher success rates are seen in timeframes less than 3 weeks from symptom onset or less than 6 weeks postindex surgery.[33] Indeed, there is no evidence-based time interval that divides acute and chronic PJI due to the natural history of infection being on a continuum and therefore time is not the sole factor in deciding treatment course. Current strategies available for PJI treatment include combinations of antibiotic treatment, mechanical disruption, irrigation and debridement (I&D), and removal of the infected prosthesis in either single-stage or two-stage procedure (Figure 1).

- DAIR is a combination of I&D with antibiotics plus exchange of modular components. DAIR is a common treatment strategy for acute PJI mainly due to the theoretical early state of the infection. Biofilm-associated bacteria are still in their early stages and antibiotics may still be effective.[34] DAIR is also preferred for patients with health complications or containing megaprostheses where remaining reconstructive surgery alternatives are limited. During DAIR, multiple irrigation protocols and solutions are being used; however, they are not standardized. Most frequently used solutions include normal saline, providone-iodine, chlorhexadine gluconate, hydrogen peroxide, bacitracin, and hypochlorite (refer to this review for an overview of commonly used lavage solutions and their efficacy[35]). A combination can also be used, but certain combinations can be toxic and most are cytotoxic at therapeutic doses where biofilm eradication is apparent.[35–38] Even with these factors in mind, failure rates using DAIR for knee and hip PJI range from 31% to 63%.[39,40]
- One-stage revision is a common procedure in Europe and gaining popularity in the United States. In one-stage revision, radical

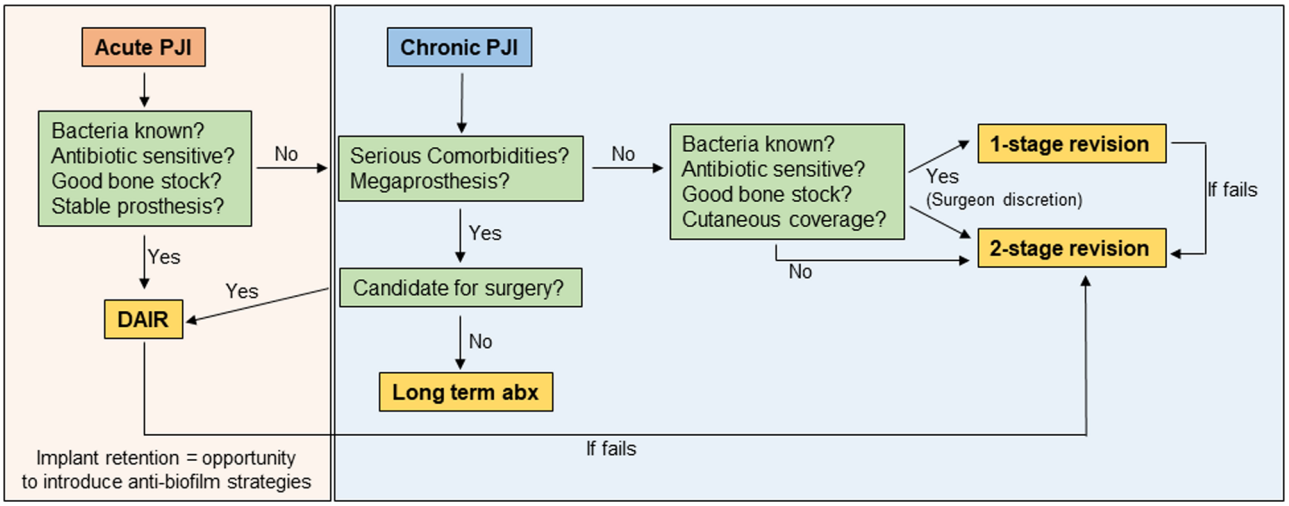

FIGURE 1 Current treatment options for PJI. Treatment options are dependent on multiple factors including duration, comorbidities, and bacteria identification. PJI, periprosthetic joint infection.

synovectomy, extensive debridement of the soft tissue, and all prosthetic components are replaced and the patient is placed on systemic antibiotics.[41] Many factors come into play when deciding whether a one-stage exchange is the best option for the patient—ample soft tissue, minimal bone loss, and bacterial identification and susceptibility to antibiotics is key.[42–44] Indeed, susceptibility to antibiotics alone is a cause for concern using this treatment in the United States as methicillin-resistant *S. aureus* (MRSA) is a common pathogen in PJI.[8] Failure rates for one-stage revisions range from 6% to 17%.[45,46]

- Two-stage revision is the gold standard in the United States where the first stage involves resection of infected tissue, removal of all components of the prosthesis, and placement of an antibiotic-impregnated cement spacer (static or articulating) with months of antibiotics.[47–49] During the second surgery, spacer is removed, joint debrided, and a new prosthesis is placed. Failure rates for two-stage revisions range from 8% to 20%.[45,46]

Despite a number of options, overall surgical failure rates range from 8% to 63%, with higher failure rates seen when retaining implant components.[39,40,50] Of note, these failure rates do not account for patients' quality of life, those that do not continue to second-stage revisions, lost to follow-up, and amputations and failure rates of 40% for staged revisions have been reported when including these factors.[51] Therefore, new treatment modalities that work outside the typical PJI strategies need to be developed. All treatments rely heavily on antibiotics which mostly target five biosynthetic processes involved in actively growing bacteria—protein, RNA, DNA, peptidoglycan, and folic acid synthesis.[52] This coupled with the differential penetration distances into a biofilm that antibiotics display, explains how some drugs may fail to completely eradicate biofilm-associated bacteria.[53] In order for antibiotics to be more effective, antibiofilm treatments need to be utilized to break through the protective biofilm barrier, thus releasing bacteria from the quiescent, metabolically low activity state. Indeed, in chronic wound infection models where biofilm is present in up to 60% of cases, the use of anti-biofilm treatments transformed previously nonhealable wounds into healable wounds with a 25% reduction in antibiotic use[54,55] showing that a combined attack may be promising to target PJI.

Therefore, the following literature review aims to identify various strategies currently in development to combat biofilm, with emphasis on those strategies that have shown promise against bacteria commonly associated with PJI including *S. aureus*.[8] Many studies have focused on the effectiveness of agents at various stages of biofilm formation, including bacterial adhesion, maturation, and dispersal. While these studies are useful to limit infection at early stages, the focus of this review is on mature biofilm treatments as these are most relevant to biofilm-associated PJI. Of note, whether these specific treatments mentioned in this review also target bacteria within the bone, intracellular bacteria, and those found in abscess communities has not been determined. A majority of readouts in these studies rely on colony-forming unit (CFU) counting after sonication of implants and qualitative scanning electron microscopy (SEM) and can only conclude that these methods decrease the bacterial load in the system without quantitatively assessing biofilm coverage. While a staged revision, where removal of all implanted components is replaced, can make biofilm clearance on implants irrelevant, the focus of this review is to emphasize strategies that can promote implant retention. These strategies can be used in parallel with other treatments that focus on bone and tissue infections to improve quality of life and decrease the economic burden associated with PJI treatment.

4 | ELECTROCHEMICAL METHODS

Treatment via electrochemical methods is based on the application of an electrical current to an electrically conductive surface like titanium where ions like hydrogen or hydroxide are released.[56] With the effort to decrease the use of antibiotics due to antibiotic resistance, this treatment method is promising as ions have shown antimicrobial effects against various gram-negative and gram-positive bacteria (Table 1).

4.1 | Cathodic-voltage-controlled electrical stimulation (CVCES)

CVCES of titanium, which is a commonly used metal for orthopedic and dental devices, has been shown to both prevent and eradicate implant infection with both MRSA and *P. aeruginosa* when treated for 24 h in vitro at −1.8 V.[56–58] Similar results were also seen in vivo in a rat model of PJI where MRSA CFU were reduced by 98% on a titanium rod into the shoulder joint when treated for 1 h with no discernable tissue toxicity via H&E staining.[56,58] This decrease in biofilm-associated bacteria as well as planktonic bacteria viability was thought to be due to an alkaline environment generated during treatment, with pH rising as high as 14, where optimal bacterial growth is around pH 2–3.[59] Indeed, combination therapy with vancomycin had a synergistic effect in vivo on the implant, surrounding tissue, and synovial fluid with reduction by 99.8%.[58] Bacterial eradication was not seen using this method but with combined therapies, may prove as a useful treatment strategy for PJI.

4.2 | Electrochemical scaffolds (e-scaffolds)

Electrochemical scaffolds (e-scaffolds) are a recently developed technique where a conductive carbon fabric is overlaid onto the biofilm infected surface, polarized at −600 mV, and reduces oxygen to produce a sustained low concentration of H_2O_2 near the biofilm surface.[66,67] This H_2O_2 damages bacterial DNA and causes oxidative damage to bacterial proteins and lipids leading to defects in cell membrane integrity.[60,68] With a second-generation e-scaffold that produces hypochlorous acid (HOCl), HOCl generation at 17 mM has

TABLE 1 Electrochemical antibiofilm methods.

Method	Bacterial strain	Mechanism	Results	References
Cathodic-voltage-controlled electrical stimulation (CVCES)[a]	MRSA *P. aeruginosa*	Alkaline pH	In vitro: Bacteria toxicity and decreased biofilm In vivo: Rat shoulder model (98% biofilm-associated bacteria reduction), nontoxic to host tissue	[56–59]
Electrochemical scaffolds (e-scaffolds)	*S. aureus*	H_2O_2 production	In vitro: 2–3-fold viable bacteria decrease	[60]
	S. aureus	HOCl production	In vitro: 7-fold viable bacteria decrease	[61]
	A. baumannii *P. aeruginosa*		Ex vivo: positive results in procine dermal explants, nontoxic to host tissue	
Electrical currents	*S. aureus* *P. aeruginosa*	Alkaline pH	In vitro: 4–5-fold viable bacteria decrease. Requires days of treatment	[62]
Hyperthermia[a]	*S. aureus* *P. aeruginosa*	Bacteria release from biofilm, membrane disruption	In vitro: controlled heating releases bacteria from biofilm with limited tissue toxicity	[28,63–65]

Abbreviation: MRSA, methicillin-resistant *S. aureus*.

[a]Better outcomes with combination antibiotics therapy.

shown productive results with a 7-log decrease in viable *S. aureus* after 3 h of treatment in vitro.[61] Similar results were seen when used on gram-negative *Acinetobacter baumannii* and *P. aeruginosa* biofilms when treated with the HOCl e-scaffold and required less time to decrease CFU below the limit of detection than *S. aureus* biofilm. Not surprisingly, the addition of exogenous HOCl had similar effects in decreased biofilm-associated bacteria viability. HOCl is thought to cause bacterial cell wall damage, and inhibit ATP production, DNA replication, and protein translation but is not cytotoxic to mammalian cells when tested on ex vivo porcine dermal explants.[61] These studies show promise but further work in an in vivo animal model and whether direct contact is required for its microbiological effects needs to be addressed.

4.3 | Electrical currents

Electrical currents have been proposed to promote biofilm detachment due to disruption of the chemical nature of biofilm–biomaterial interaction including Van der Waals forces, acid–base interactions, and electrostatic forces.[62] Since most bacteria and biomaterials are negatively charged and are repulsive in nature, whether an electrical charge is able to enhance the repulsive forces thereby destabilizing the biofilm–biomaterial interface has been proposed.[62] With *S. aureus* biofilm exposed to 2000 mA through stainless steel electrodes for 2 days in vitro, a 4–5-log reduction in CFU was observed and may be due to alkaline pH levels observed during treatment as previously described in other electrochemical methods.[59,62] Of note, similar results were observed when gram-negative *P. aeruginosa* was treated with low-intensity electrical current. While these in vitro experiments required days of continuous electric current treatment, it does support the concept that electrochemical methods warrant further investigation in biofilm clearance.

4.4 | Hyperthermia

Hyperthermia has been shown to decrease biofilm attachment by both *P. aeruginosa* and *S. aureus*.[63] Early heat shock iterations were quite damaging to surrounding tissues; therefore, newer successions have included the use of laser-induced hyperthermia.[28,63] Hyperthermia is achieved via heating of conductive nanoparticles or through alternating magnetic fields and has led to decreased biofilm burden via CFU with decreased cytotoxicity to surrounding tissues with even greater efficacy when combined with antibiotics.[64,65] Indeed, an increased number of suspended cells were also present after treatment that can be further targeted by antibiotics.[28,63,65,69–71]

5 | SMALL MOLECULE INHIBITION

The use of small molecules has been leading the field in targeting specific pathways in biofilm formation, quorum sensing, second messenger signaling, maturation, and fully mature biofilm maintenance.[72,73] Cyclic nucleotides including cyclic adenosine monophosphate and cyclic guanosine monophosphate are well-known signaling molecules in eukaryotes and have been shown to be important also in bacteria signaling pathways (Table 2).

5.1 | c-di-GMP (cyclic dinucleotide GMP)

c-di-GMP is a second messenger molecule that is ubiquitous in bacteria with conserved GGDEF (Gly-Gly-Asp-Glu-Phe) domain and levels change based on environmental and intracellular signals. Of note, although *S. aureus* expresses the GGDEF motif, it has been reported that c-di-GMP signaling does not exist but a related GGDEF domain protein, GdpS, does

TABLE 2 Small molecule antibiofilm methods.

Method	Bacterial strain	Mechanism	Results	References
c-di-GMP	*S. aureus*	Complexes and sequesters second messengers	In vitro: 75% reduction in biofilm	[74–78]
	P. aeruginosa		In vitro: low levels facilitate dispersal	
c-di-AMP	*S. aureus*	Extrinsic	In vitro: promotes persistence by inducing IFNβ production from anti-inflammatory macrophages	[79,80]
Nitric oxide (NO)[a]	*S. aureus*	Biofilm dispersal	In vitro: long-lived NO mimic CTEMPO— increased dispersal, no bactericidal effects	[81–83]

[a]Better outcomes with combination antibiotics therapy.

regulate biofilm in *S. aureus*.[74,75] While much of the work with c-di-GMP has focused on its inhibitory effects in biofilm formation, in vitro experiments using clinical isolate DK825 *S. aureus* have shown a 75% reduction in preformed biofilms at treatment doses of 200 μM.[76] A putative mechanism of action suggests that c-di-GMP either complexes or sequesters other signaling molecules important in biofilm formation and maintenance or changes protein expression. In other studies using bacteria including *P. aeruginosa*, c-di-GMP is expressed at high levels to promote biofilm formation and low levels facilitate biofilm dispersal.[77,78]

5.2 | c-di-AMP (cyclic diadenylate monophosphate)

c-di-AMP is found in gram-positive bacteria but absent in gram-negative bacteria.[84] This second messenger has contrasting roles in the literature. The elevated expression has been shown to increase some cell wall-active antimicrobials in *S. aureus* while it has also been shown that either elevated or decreased c-di-AMP signaling is involved in biofilm formation, but little work has been done on the role of c-di-AMP signaling in preformed biofilms.

Interestingly, extrinsic roles of c-di-AMP have been shown to induce bystander macrophages into an anti-inflammatory phenotype that express type I interferon (IFNβ) to promote persistence.[79,80] Sequestering secreted c-di-AMP from mature biofilms may inhibit this anti-inflammatory conversion of macrophages and reinvigorate the immune response to the bacterial infection. Nevertheless, whether there is a role for c-di-AMP intrinsically that promotes biofilm survival still needs to be investigated.

5.3 | Nitric oxide (NO)

Nitric oxide (NO) has been shown to inhibit biofilm formation and prompt biofilm dispersal in many gram-negative and gram-positive bacteria.[81,82] While NO has shown promise in biofilm dispersal, its gaseous reactive state and short half-life (0.1−5 s) has made it difficult to develop therapies.[85] Nitroxides are long-lived, stable free radical species that are crystalline at room temperature. CTEMPO is a structural mimic of NO with a disubstituted nitrogen atom linked to a univalent oxygen atom.[83,86] A nitroxide, 4-carboxy-2,2,6,6-tetramethylpiperidin-1-yloxyl (CTEMPO), enhanced *S. aureus* dispersal in vitro but was not involved in bacterial killing. Combination therapy by linking CTEMPO to ciprofloxacin was able to both disperse bacteria from the biofilm and secondly kill bacteria as they were no longer protected by the biofilm.[83] When linked to fluorescence to monitor biofilm permeability by confocal laser scanning microscopy, this nitroxide was able to penetrate deep within the biofilm and was not cytotoxic to human cells.[83]

6 | BIOLOGICS

6.1 | Polyclonal and monoclonal antibodies

Polyclonal and monoclonal antibodies have come to the forefront initially to treat rheumatologic diseases. Recently, drug companies have begun focusing on developing biologics for many nonrheumatologic diseases.[87,88] Effectiveness in protecting against biofilm infections using various monoclonal/polyclonal antibodies has been shown in vitro and in animal models but very few have seen success as a clinical treatment.[89] Clinical trials of monoclonal antibodies targeting several components of the cell wall or bacteria-associated toxins based on preclinical studies, while safe, were ineffective.[89,90] Testing of additional targets is still underway (Table 3).

6.1.1 | DNABII

Polyclonal antisera against DNABII, lynchpin proteins involved in eDNA structural integrity that are expressed by many different biofilm-producing bacterial strains, have proved as a promising target for biofilm dispersal. This antisera (against DNABII from *Escherichia coli*) was able to bind free DNABII proteins, sequestering them away from eDNA association and leading to structural collapse of the biofilm matrix and release of bacteria when tested with *Haemophilus influenza* in vitro.[91] Further work was completed where monoclonal antibodies against various epitopes of DNABII were generated and were able to disrupt biofilm structure in both *S. aureus* and *P. aeruginosa*.[92] Of note, this mechanism is a passive mechanism that requires active biofilm remodeling for its effect. Another monoclonal antibody, TRL1068 specific for an epitope on DNABII, was also effective against MRSA in vitro and in in vivo models of murine tissue cage infection and rat infective

TABLE 3 Biologics including antibodies and antimicrobial peptides for antibiofilm targeting.

Method	Bacterial strain	Mechanism	Results	References
Antibodies				
DNABII antisera	*S. aureus*	Sequestration of DNABII from eDNA	In vitro: biofilm structure disruption—requires active biofilm remodeling	[91–94]
TRL1068[a]	*P. aeruginosa* MRSA		In vivo: murine tissue cage infection and rate infective endocarditis effectiveness	
Anti-Atl	MRSA	Inhibits binary fission Increased phagocytosis by macrophages	Ex vivo: humans with MRSA PJI with high IgG levels of anti-Atl had better outcomes than MRSA PJI with low levels of anti-Atl In vivo: mouse MRSA infection protection	[95,96]
Antimicrobial Peptides				
LL-37	*S. aureus*	Unknown Putative: antimicrobial or downregulation of quorum-sensing for biofilm maintenance	In vivo: 4-log reduction of biofilm-associated bacterial growth on chromium cobalt	[97,98]
D-Bac8c	*S. aureus* MRSA	Unknown	In vivo: rat jugular vein catheter infection model—5-day treatment resulted in no viable bacteria isolated from catheter	[99]
1018-K6	*S. aureus* MRSA	Cell membrane breakdown	In vitro: used in the context of food surfaces with no viable bacteria in minutes	[100]
pepR	*S. aureus*	Unknown	In vitro: 15%–20% biofilm-associated bactericidal effects seen with a single treatment. Additional treatments increased effectiveness to 95%–99%	[101]
PLG0206	*S. epidermidis* MRSA *S. aureus* *H. parainfluenzae*	Unknown	Phase 1 clinical trial: well-tolerated up to 1 mg/ml in healthy controls intravenously Ex vivo: human infected explants treated for 15 min with 4-log reduction (some treated with antibiotics before explant)	[102,103]

Abbreviation: eDNA, extracellular DNA; MRSA, methicillin-resistant *S. aureus*.
[a]Better outcomes with combination antibiotics therapy

endocarditis.[93,94] Once again, better efficacy was observed in combination with antibiotics.[93,94]

6.1.2 | Autolysin

Interestingly, a subset of PJI patients with high serum IgG levels against an adhesin named autolysin (Atl) was able to recover from MRSA PJI while those with low anti-Atl IgG levels had worse outcomes.[95] This prompted the synthesis of an anti-Atl antibody (against the glucoaminidase subunit of Atl) and this was able to protect mice via inhibiting *S. aureus* binary fission and increasing opsonophagocytosis by macrophages.[96]

6.2 | Antimicrobial peptides (AMPs)

AMPs are molecules produced by different organisms that target gram-positive and gram-negative bacteria, viruses, and fungi.[104] These AMPs are small, cationic, and amphipathic and have recently been appreciated as a possible treatment for bacterial biofilm.[105] AMPs act through membrane disruption or seeking intracellular targets making them useful in biofilm scenarios where slow growth is seen.[101,106] With the generation of synthetic AMPs, to overcome issues with charge and stability,[107] high throughput antibiofilm screening assays are able to be performed to isolate those that have potential use therapeutically.

6.2.1 | LL-37

LL-37 is an AMP that has shown high potency against *S. aureus* biofilm when grown in vivo on chromium cobalt, a common orthopedic implant material.[97,98] While useful, enzymes secreted by bacteria including aureolysin and V8 protease also can degrade LL-37.[97,98] This peptide is also cytotoxic to immune cells in its native form. Shorter derivatives are currently being synthesized that are hoped to decrease degradation and cytotoxicity.[107]

6.2.2 | D-Bac8c

D-Bac8c is a synthetic AMP that was identified through high throughput anti-biofilm screening. This peptide was synthesized as a D-enantiomer which has been one of the modifications associated with increased success with AMPs against *S. aureus*.[99,108] D-Bac8c has low cytotoxicity and overall does not induce expression of proinflammatory cytokines. When used in vivo in a rat jugular vein catheter infection model, a 5-day continuous treatment using a catheter lock solution changed daily, resulted in no viable bacteria isolated from *S. aureus* biofilm.[99]

6.2.3 | 1018-K6

1018-K6 is a synthetically derived AMP that has been shown to both prevent and eradicate established biofilm by both *S. aureus* and MRSA in the context of food safety. Established biofilm was eradicated in minutes via cell membrane breakdown. While this AMP has only been tested in the context of food safety where bacterial biofilms can form on surfaces of food processing areas, this has the potential to be engineered for other uses.[100]

6.2.4 | Pepr

PepR is a synthetic peptide that corresponds to the amino acid residues 67–100 from the Dengue virus capsid protein that can target both gram-positive and gram-negative planktonic bacteria and preformed *S. aureus* biofilm when tested in vitro. Bacterial killing was seen in a dose- and time-dependent manner and when biofilm was treated with saturating concentrations, diffusion into deeper layers of the biofilm was also seen, where two treatments were required for over 95% biofilm clearance.[101]

6.2.5 | PLG0206

PLG0206 is a broad spectrum, rapidly acting engineered peptide that is active against antibiotic-tolerant biofilms. In an ex vivo trial, 17 explants taken from two-stage revisions were incubated with 1 mg/ml PLG0206 for 15 min where a 4-log reduction was observed.[102] This cationic peptide has gone through Phase I trials where intravenous PLG0206 was well tolerated by healthy controls thus warranting further development and clinical trials (NCT05137314).[103,109]

7 | TARGETING BIOFILM MEMBRANE COMPONENTS

The idea of targeting biofilm membrane components to inevitably eradicate biofilm infection is not a new concept. Multiple enzymes and endogenous disassembly molecules have been tested that target membrane components, specifically polysaccharides and eDNA (Table 4).

7.1 | Polysaccharides

Polysaccharides like poly-*N*-acetylglucosamine (PNAG) play a key role in biofilm formation and accumulation.[124,125] The *icaADBC* locus has been identified to code for PNAG and is present in a majority of staphylococcal isolates from chronic wounds and infected foreign bodies.[126–128]

7.1.1 | Dispersin B

This molecule has recently been isolated from the oral pathogen *Actinobacillus actinomycetemcomitans* that has PNAG-hydrolyzing activity.[110–112] It has been shown to eradicate *S. epidermidis* isolated from infected catheters[110,111] and from bacterial strains with increased PNAG composition but had no effect on *S. aureus* biofilm which are PNAG negative.[114] Therefore, this treatment strategy is PNAG-dependent.

7.1.2 | Periodate (HIO4 or NAIO4)

An anion that contains iodine and oxygen that can break down biofilms containing PNAG produced by *E. coli*[113] and some strains of *S. epidermidis*[115] but ineffective against *S. aureus* isolates with minimal PNAG containing biofilm.[114] Of note, some bacterial strains that produce biofilm with high PNAG levels were not susceptible to periodate treatment possibly due to a required periodate hydrolyzing step making PNAG inert to treatment.[114]

7.1.3 | Proteinase K

An extracellular serine protease that is stable in a broad range of conditions including pH, buffer salts, detergents, and temperature.[116] It is produced by *S. aureus* and contributes to the disassembly process for biofilm detachment. It has been shown to promote detachment of staphylococcal biofilms containing two carbohydrate components PNAG and teichoic acid (TA) including *S. aureus* and *S. epidermidis* isolated from orthopedic prosthesis infections.[114] While proteinase K did work on biofilm dispersal, others have reported that its efficacy was actually less dependent on the PNAG and TA composition of the biofilm, which was variable between clinical isolates.[114,129]

Biofilm-associated protein (Bap) is a cell surface anchor protein and has a putative role in eDNA retention that has functions in both biofilm formation as well as dispersal. Only recently, *bap* gene expression has been appreciated in the context of human nosocomial infections. Proteinase K is also able to exert its biofilm diminishing capabilities in a *bap*-dependent manner as *bap*-negative *S. aureus* strains were resistant to antibiofilm treatment of 24–48 h-old biofilms.[117,118]

TABLE 4 Antibiofilm methods targeting membrane components.

Method	Bacterial strain	Mechanism	Results	References
Polysaccharides				
Dispersin B	*S. epidermidis*	PNAG hydrolyzing activity	In vitro: Some showed positive results in dispersing biofilm but dependent on PNAG composition in biofilm	[110–113]
			In vivo: positive results in catheters and chronic wound infections	
Periodate (HIO4 or NAIO4)	*E. coli*	Breakdown via iodine and oxygen	In vitro: Dependent on PNAG composition in biofilm. Anion mechanism ineffective in some PNAG-positive strains due to acidic hydrolysis	[113–115]
	S. epidermidis			
Proteinase K[a]	*S. aureus*	Extracellular serine protease, part of disassembly process	Ex vivo: targets PNAG and teichoic acid (TA) on orthopedic devices (may not be PNAG and TA dependent)	[114,116]
	S. epidermidis		In vitro: Bap-dependent proteinase-K biofilm breakdown	[117,118]
		Anchor protein breakdown	Ex vivo (bovine mastitis): Bap-dependent biofilm dispersal	
D-amino acids	*S. aureus*	Amyloid fiber breakdown	In vitro: nanomolar concentrations can eradicate ~70% of biofilm. Combination D-amino acids and hyperthermia treatment shows no viable bacteria after 2 h	[64,119,120]
eDNA				
DNase I[a]	*S. aureus*	DNA degrading enzyme	In vitro: treatment leads to biofilm detachment in minutes	[121,122]
	S. epidermidis		In vivo: in cystic fibrosis, used in combination with antibiotics for younger biofilms but lose effectiveness with older	
NucB	Gram-negative	DNA degrading enzyme	In vitro: Lower concentrations (3 ng/ml) compared to DNase needed for antibiofilm effect, works on gram-negative and gram-positive bacteria	[123]
	Gram-positive			
	S. aureus		Ex vivo: works against various *Staphylococcal* species isolated from chronic rhinosinusitis	
	Staphylococcal species			

Abbreviation: eDNA, extracellular DNA; PNAG, poly-*N*-acetylglucosamine.

[a]Better outcomes with combination antibiotics therapy.

7.1.4 | D-amino acids

D-amino acids are nontoxic isomers that are used in the biofilm disassembly process by bacteria where these D-amino acids incorporate into the cell wall and lead to amyloid fiber breakdown.[119,120] D-amino acids also have a role in inhibiting bacterial adhesion and biofilm assembly showing its diverse role in multiple stages of biofilm process.[130,131] Studies have shown that D-amino acids (D-trp, D-phe, D-tyr) at nanomolar concentrations are able to eradicate 70% of *S. aureus* biofilm in vitro biofilm assays.[64,132] With a combination D-amino acids plus hyperthermia (PhotothermAA gel) using conductive nanoparticles in a glycol chitin hydrogel, no viable bacteria were observed after 2-h treatment.[64,132]

7.2 | eDNA

eDNA is made by bacteria in biofilm and produced by different mechanisms depending on bacteria. *S. aureus* eDNA is released via autolysis mediated by murein hydrolase and is a key component in the biofilm matrix for its structural integrity.[133] Therefore, this is a promising target for biofilm destabilization.

7.2.1 | DNase I

DNase has been a common treatment for cystic fibrosis infections where a combination of antibiotics with recombinant human DNase I (rhDNase I) is prescribed.[121,122] Younger biofilms are easier to remove using DNase treatment but lose their effectiveness as biofilms age. A possible explanation for this increased resistance to DNase degradation is due to EPS interactions that may shield eDNA from DNase activity.[134] Similar work using rhDNase I against both *S. aureus* and *S. epidermidis* biofilms was able to promote biofilm detachment in minutes.[122]

7.2.2 | NucB

A bacterial deoxyribonyclease isolated from *Bacillus licheniformis* is able to decrease biofilm burden of gram-negative, gram-positive, and multiple *S. aureus* variants, and other *Staphylococcal* species isolated from patients with chronic rhinosinusitis. Low concentrations of NucB (3 ng/ml) compared to concentrations needed for biofilm disruption by DNase I (15 ng/ml) suggest that this nuclease is better adapted to target eDNA at lower concentrations.[123]

8 | ENDOGENOUS MOLECULES/VIRUSES THAT TARGET BACTERIA

All species have developed ways to specifically target and defend themselves. Commensal bacteria live symbiotically and have developed mechanisms to inhibit the growth of pathogenic or opportunistic bacteria that take advantage of a breakdown of the immune system or changes in the flora composition. Viruses have developed ways to specifically target certain bacterial strains. This section focuses on the molecules and viral systems that target bacteria specifically (Table 5).

8.1 | Esp

Esp is a serine protease produced by *S. epidermidis* that directly inhibits the formation and also destroys mature biofilm produced by *S. aureus* in a time-dependent manner. Although not bactericidal on its own, Esp plus the antimicrobial peptide human beta-defensin 2 (hBD2), secreted by keratinocytes, act synergistically to decrease bacterial survival of *S. aureus*-associated biofilm.[135]

8.2 | 3–7-kDa-sized molecule

A 3–7-kDa-sized molecule was discovered by Glatthardt et al.[136] that is secreted by *S. epidermidis*. It inhibits both methicillin-sensitive *S. aureus* and MRSA biofilm formation and reduces established biofilm by 7.2%–58.8%. While the exact identity of the molecule has yet to be discovered, it is hydrophobic and heat, proteinase K, trypsin, sodium periodate, and protease inhibitor-resistant. RNAseq analysis and confirmation via real-time quantitative PCR (RT-qPCR) showed its downstream targets to include the upregulation of *icaR*, an important negative regulator of the biofilm polysaccharide PNAG.[136]

8.3 | *Cis* 2-decenoic acid (C2DA)

C2DA is a medium-chain chemical messenger produced by *P. aeruginosa* that signals biofilm dispersal in both gram-negative and gram-positive bacteria.[137] Recently, studies have combined C2DA with lipid nanoparticles for easier penetration into biofilms with variable results where *S. epidermidis* biofilms were more susceptible compared to *S. aureus*, where nanoparticles had no effect.[138] Addition of rifampin antibiotics to C2DA had a positive effect against *S. epidermidis* and *S. aureus*.[138]

8.4 | Bacteriophages

Bacteriophages are viruses that specifically infect bacteria, where lytic phages infect, propagate within the cell, and lyse host cells to release phages to infect neighboring cells. Phage therapy has seen positive results in both planktonic and biofilm-associated infection.[139,140,145] In vitro, *P. aeruginosa* mature biofilm infected with a *P. aeruginosa* phage cocktail reduced both biomass and bacterial count by greater than 4-logs. Indeed, combination treatment with antibiotics showed an increased effectiveness in reducing biofilm. In vivo, both in a rabbit model of MRSA osteomyelitis and a mouse mastitis model, *S. aureus* infection was significantly reduced after treatment.[141,142] Nevertheless, clinical use of phage treatments has been on a case-by-case basis where adjunct therapy with antibiotics has had variable outcomes. In some cases,

TABLE 5 Antibiofilm methods produced by other bacteria/viruses.

Method	Bacterial strain	Mechanism	Results	References
Esp	*S. aureus*	Serine protease produced by *S. epidermidis*	In vitro: destroys mature biofilm in a time-dependent manner	[135]
			[a]used synergistically with antimicrobial peptide human beta-defensin 2(hBD2) to decrease survival and biofilm attachment	
Unidentified 3-10 kDa molecule	*S. aureus* MRSA	Secreted molecule by *S. epidermidis*, regulator of PNAG production	In vitro: inhibits biofilm formation and reduces established biofilm	[136]
Cis-2-decenoic acid (C2DA)[a]	*S. epidermidis* *S. aureus*	Small molecule produced by *P. aeruginosa*, biofilm dispersal	In vitro: more effective when encapsulated in lipid nanoparticles for *S. epidermidis* while free C2DA was more effective against *S. aureus*	[137,138]
Bacteriophages[a]	*S. aureus* MRSA *P. aeruginosa* *K. pneumoniae*	Infects bacteria and lyse cells	In vitro: *P. aeruginosa* 4-log decrease using phage cocktail In vivo: rabbit osteomyelitis and murine mastitis infections cleared with phage treatment Clinical studies: Case reports with variable results with antibiotic combination	[139–143]
PlySs2[a]	*S. aureus*	Peptidoglycan hydrolyzing activity	In vitro: *S. aureus* 2.5-log decrease when treated for 4 h of 2-week-old biofilm In vivo: *S. aureus* synergistic 1-fold decrease when treated with vancomycin in comparison to vancomycin alone in a murine model of PJI plus DAIR	[144]

Abbreviations: DAIR, debridement, antibiotics, and implant retention; PNAG, poly-*N*-acetylglucosamine.

[a]Better outcomes with combination antibiotics therapy.

antibiotics and phage treatment have shown antagonistic effects in the case of a *Klebsiella pneumonia* knee infection treated with phages and minocycline.[143]

8.5 | PlySs2

PlySs2 is a bacteriophage-derived lysin with peptidoglycan hydrolyzing activity that has been shown to decrease *S. aureus* biofilm burden after treatment both in vitro and in vivo in a murine model of PJI with DAIR treatment.[144] Combination of PlySs2 and vancomycin treatment showed a slight synergistic effect with a 0.5–1-log but whether this is clinically significant requires further testing.

9 | DRUG DELIVERY SYSTEMS WITH POTENTIAL USE IN ANTIBIOFILM TREATMENTS

The use of hydrogels as delivery systems for the elution of various substances including synthetic peptides, proteins, and antibiotics has shown some promise. Defensive antibacterial coating (DAC) is a hydrogel composed of two bioresorbable polymers, hyaluronic acid and poly-lactic acid.[146] A majority of work on DAC has focused on its use as an antibacterial coating but preliminary studies have shown increased antibiofilm properties when DAC was incubated with vancomycin or gentamycin for minimum 2 h against both *S. aureus* and *S. epidermidis*,[147] although the mechanism of action was not explored. Glycol chitin hydrogel is also being developed as a carrier system for two antibiofilm methods mentioned previously, D-AAs and hyperthermia, that has shown no viable bacteria on titanium discs in vitro.[64]

10 | CONCLUSIONS

While not a comprehensive review of the entire infection clearance and prevention literature, this review focused on literature relevant to the bacterial strains and strategies that could be potential antibiofilm treatments for PJI in the setting of retained components. Research into antibacterial coatings on implants, bacterial immunizations, and inhibiting early stages of bacterial infection and adhesion may one day come into fruition where biofilm-related infections on hardware are a thing of the past, but until then, treatment strategies need to target established infections.

AUTHOR CONTRIBUTIONS

This review was conceived by Anabelle Visperas, Alison K. Klika, and Nicolas S. Piuzzi. The review was written by Anabelle Visperas and Daniel Santana with additional expertise on infections from Carlos Higuera-Rueda and Nicolas S. Piuzzi. The manuscript was revised by Alison K. Klika, Carlos Higuera-Rueda, and Nicolas S. Piuzzi. All authors have read and approved the final submitted manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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