

# Bacterial and Fungal Biofilm Infections

A. Simon Lynch and Gregory T. Robertson

Cumbre Pharmaceuticals Inc., Dallas, Texas 75235-2304;  
email: slynch@cumbrepharma.com, greg.robertson@cumbrepharma.com

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## Key Words

antibiotic, indwelling medical device, antibiotic tolerance,  
persistent infection, staphylococcal infections, antibiotic resistance

## Abstract

Biofilms are communal structures of microorganisms encased in an exopolymeric coat that form on both natural and abiotic surfaces and have been associated with a variety of persistent infections that respond poorly to conventional antibiotic chemotherapy. Biofilm infections of certain indwelling medical devices by common pathogens such as staphylococci are not only associated with increased morbidity and mortality but are also significant contributors to the emergence and dissemination of antibiotic resistance traits in the nosocomial setting. Current treatment paradigms for biofilm-associated infections of semipermanent indwelling devices typically involve surgical replacement of the device combined with long-term antibiotic therapy and incur high health care costs. This review summarizes the existing data relating to the nature, prevalence, and treatment of biofilm-associated infections and highlights experimental approaches and therapies that are being pursued toward more effective treatments.

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**IMD:** indwelling medical device

**FBI:** foreign body infection

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## INTRODUCTION

In their natural environments, most bacterial and fungal species alternate between planktonic (free-living) and sessile states in response to environmental stimuli such as the availability of essential nutrients. Transition to growth in a sessile state frequently occurs in response to nutrient limitation and is thought to reflect a developmental switch to a perseverance mode wherein a biopolymer-encased, structured community of cells—a biofilm—forms on a biotic or abiotic surface. Because the availability of nutrients often parallels the abundance of competing organisms, the developmental switch to the biofilm state is commonly regulated by inter- and intraspecies quorum-sensing mechanisms.

The formation and maturation of a biofilm involve a number of transitional states that span the initial attachment phase and the terminal dispersal phase (1) and have been characterized through genome-wide expression profiling and proteomic analysis. Such efforts have identified a number of proteins that play specialized roles in the biofilm phase and have revealed more comprehensive changes in gene expression that reflect a downshift in overall metabolic activity consistent with enhanced perseverance (2).

At the phenotypic level, a microbial biofilm can also be characterized as a communal population of cells that exhibits tolerance (or insensitivity) to antimicrobial agents that are active on the cells of the biofilm once dispersed into their planktonic state. In situations where the planktonic susceptibility of a pathogen to an antibiotic is known, this type of definition may be informative in predicting whether an ongoing infection may involve a biofilm component.

In addition to the phenotypic response of biofilms to antibiotic challenge, these multicellular structures also exhibit a genotypic response that is of clinical significance in the development and spread of antibiotic resistance traits in nosocomial pathogens. This genotypic response can include the *de novo*

emergence of antibiotic resistance through elevated mutation rates, as well as an enhanced propensity of cells in biofilms to exchange genetic elements bearing antibiotic resistance traits through intra- and interspecies transfer mechanisms (3, 4).

## BIOFILM-ASSOCIATED INFECTIONS: DISEASE STATES, CAUSATIVE PATHOGENS, AND IMPACT ON HEALTH CARE COSTS

Definitive studies to satisfy Koch's postulates regarding the essentiality of biofilms as specific etiological agents of disease are lacking (2). In light of the inherent difficulties in establishing an unambiguous role for biofilm-induced pathogenesis, a minimal set of criteria was recently proposed for determining a biofilm etiology of an infection. These criteria include the presence of substratum-adherent, matrix-encased clusters of bacteria that exhibit phenotypic resistance to antibiotics active on the composite planktonic cells (5). Overall, the most persuasive existing evidence for a specific role for biofilms in human disease pathogenesis comes from direct observational studies wherein microscopic methods have been employed to identify biofilm structures either at infection sites *in situ* or on infected tissues or devices freshly recovered from patients.

### Foreign Body Infections

Infections that are thought to involve biofilm foci are most frequently associated with microbial colonization of the abiotic surface(s) of indwelling medical devices (IMDs) and other materials and are commonly referred to as foreign body infections (FBIs). Microscopic examination of IMDs extracted from patients, including those with FBIs refractory to antibiotic treatment, has revealed the presence of biofilm-like structures formed by bacteria and fungi in a number of studies (2). Although

clinical biofilms are typically of lower cell density than those grown *in vitro*, their overall architecture as revealed by electron microscopic methods is similar. These studies have also provided evidence for interactions of the biofilm and host tissues.

In the United States, device infections associated with low attributable mortality have been estimated to have initial rates of infection that vary from 1%–3% for mammary implants, penile implants, and joint prosthesis to 10%–30% for urinary catheters (2, 6, 7). IMDs associated with infections of moderate attributable mortality include vascular grafts (1%–5%), cardiac pacemakers (1%–7%), and central venous catheters (CVCs) (3%–8%). Infections associated with cardiac assist devices at the time of placement arise in 25%–50% of cases and attributable mortality can exceed 25% (6). However, these estimates are derived from cases of infections documented by appropriate diagnostic cultures and are probably conservative, partly owing to the limited sensitivity of available diagnostic and clinical microbiology techniques (7). Further, IMDs represent a risk factor for the hematogenous seeding of infections throughout the lifetime of the device in place, and the use of prophylactic antibiotic therapy is routine in high-risk patients prior to invasive dental or surgical procedures.

In most instances, infection is diagnosed by clinical symptoms and/or bacteremia, or through other nonsurgical cultures of local body fluids; however, such methods often yield false negative results (7). Sonication and polymerase chain reaction (PCR) amplification methods have been experimentally shown to improve the detection of biofilms on explanted orthopedic implants (8), but widespread use of such approaches would require specialized equipment and techniques not common in clinical laboratories. Other nonmicrobiologic diagnostic options, such as advanced imaging techniques, have been used in the medical diagnosis of probable biofilm infections of surgical IMDs. For example, transesophageal echocardiography has been

employed to detect biofilms associated with endocarditis on prosthetic heart valves (2), while ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have been applied with varying success to the diagnosis of deep arterial prosthetic infections (9). Although multiple radiologic techniques, particularly radioisotopic labeling with indium and technetium, have been shown to aid in the diagnosis of prosthetic joint infections and other forms of osteomyelitis, they can give false positive results more than a year after IMD implantation (10). Overall, much work remains in overcoming diagnostic challenges associated with biofilm infections of surgical implants.

For nonsurgical IMDs, such as CVCs and urinary catheters, biofilm colonization may originate either from the skin at the point of insertion, or by migration of the organism(s) through or around the catheter once implanted (2). For surgical IMDs, tissue damage and clot formation associated with surgical implantation are correlated with enhanced rates of microbial biofilm colonization (2). Delayed or late-onset orthopedic IMD infections tend to be caused by low-virulence pathogens, such as coagulase-negative staphylococci (CoNS) and *Propionibacterium acnes*, and may result from hematogenous seeding of the implant following other invasive procedures or infections (11).

**Table 1** lists the principal IMDs whose function can be compromised by biofilm colonization and the prevalent causative pathogens associated with the resulting FBIs. In many instances, colonization precedes the clinical manifestation of infection and is often sufficient to adversely affect the mechanical function of the device. Prominent pathogens most often associated with biofilm infections of IMDs are either normal commensal flora or are nosocomial in origin. Prevalent Gram-positive cocci often include CoNS, reflecting both their ubiquity as skin flora and their adherence to IMD surfaces, host tissues, and fibronectin (2, 12), and *Staphylococcus aureus*, which exists both as nasopharyngeal

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**CVC:** central venous catheter

**CoNS:** coagulase-negative staphylococci

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**Table 1 Indwelling medical devices commonly associated with biofilm infections**

Device	Prevalent causative pathogens	
	Principal	Secondary
central venous catheters	CoNS	<i>S. aureus</i> , enterococci, <i>Candida</i> spp., <i>K. pneumoniae</i> , <i>P. aeruginosa</i>
urethral catheters	<i>E. coli</i>	<i>Candida</i> spp., CoNS, <i>E. faecalis</i> , <i>P. mirabilis</i>
mechanical heart valves	CoNS	<i>S. aureus</i> , <i>Streptococcus</i> spp., GNB, enterococci, diphtheroids
ventricular assist devices	CoNS	<i>S. aureus</i> , <i>Candida</i> spp., <i>P. aeruginosa</i>
coronary stents	<i>S. aureus</i>	CoNS, <i>P. aeruginosa</i> , <i>Candida</i> spp.
neurosurgical ventricular shunts	Staphylococci	<i>Streptococcus</i> spp., <i>Corynebacterium</i> , GNB
peritoneal dialysis catheters	<i>S. aureus</i>	<i>P. aeruginosa</i> , other Gram-negative spp., <i>Candida</i> spp.
orthopedic prostheses	Staphylococci	<i>S. pneumoniae</i> , <i>Streptococcus</i> spp., <i>P. acnes</i>
fracture-fixation devices	CoNS	<i>S. aureus</i> , <i>Propionibacterium</i> spp., <i>Corynebacterium</i> , <i>Streptococcus</i> spp.
endotracheal tubes	Enteric GNB	<i>P. aeruginosa</i> , <i>Streptococcus</i> spp., <i>Staphylococcus</i> spp.
inflatable penile implants	CoNS	<i>S. aureus</i> , enteric GNB, <i>P. aeruginosa</i> , <i>Serratia</i> spp., fungi
breast implants	Staphylococci	<i>E. coli</i> , peptostreptococci, <i>C. perfringens</i> , <i>P. acnes</i>
cochlear implants	<i>S. aureus</i>	<i>P. aeruginosa</i> , <i>Streptococcus</i> spp., <i>N. meningitidis</i> , fungi

Abbreviations: CoNS, coagulase-negative staphylococci; GNB, Gram-negative bacilli.

flora and as a nosocomial pathogen. Owing to their ability to produce multiple toxins and degradative enzymes, *S. aureus* biofilm infections of IMDs tend to be more acute, promoting significant tissue damage and host immune response. In contrast, CoNS infections tend to follow a more chronic disease progression (2, 11).

Two stages of biofilm colonization have been proposed for the staphylococci: (a) the attachment phase, in which cells first associate with the IMD or with host-derived products such as fibronectin or fibrinogen that initially coat the device; and (b) the accumulation phase, in which cell-cell adhesion occurs, and the hallmark encasement of the nascent biofilm in an extracellular polymeric substance ensues (12). These two phases are genetically separable, and multiple gene products have been identified in laboratory strains as contributors to robust biofilm formation in vitro, including fibrinogen and fibronectin binding proteins (MSCRAMM family adhesins), capsular polysaccharide adhesion factors, autolysin, teichoic acids, and polysaccharide intercellular adhesin (12). In contrast, knowledge of factors involved in biofilm-specific disease

progression in clinical isolates is generally lacking.

Among fungal pathogens, *Candida albicans*, a commensal mucosal organism and opportunistic pathogen of the immunocompromised, is most commonly associated with biofilm colonization of IMDs, and the resultant candidiasis is associated with high mortality (13–16). Other opportunistic biofilm-forming *Candida* species also associated with catheter-related bloodstream infections (CRBSIs) include *C. parapsilosis*, *C. tropicalis*, *C. lusitanae*, *C. krusei*, and *C. glabrata* (15, 17). Biofilm colonization of ventricular shunt catheters, peritoneal dialysis fistulas, and cardiac valves by *Cryptococcus neoformans* has also been reported and is of particular concern in light of the growing use of ventriculo-peritoneal shunts to manage intracranial hypertension associated with cryptococcal meningoencephalitis in immunocompromised patients. Recurrent meningitis in patients with ventriculo-peritoneal shunts has also been associated with biofilm colonization by *Coccidioides immitis*. Endocarditis associated with infections of prosthetic valves and other cardiac devices by *Aspergillus* species is a growing concern in immunocompromised

**MSCRAMM:**

microbial surface components recognizing adhesive matrix molecules

**CRBSI:**

catheter-related bloodstream infection

patients, although a definitive role of biofilms has yet to be established. Overall, although *Candida* and *Aspergillus* species are the etiologic agents in only ~8% of implant infections, they are emerging as formidable pathogens with a patient survival rate in some settings as low as 50% (18).

The isolation of multiple discrete species from biofilm-colonized implants derived from patients provides the most compelling evidence of the medical importance of polymicrobial (or heterotypic) biofilms (19). Studies of polymicrobial biofilms formed by *C. albicans* and *S. epidermidis* indicate that the exopolymeric matrix produced by the fungal species may protect the bacteria against antibiotics, while the bacterial matrix protects the fungi from antifungal action. Other studies of polymicrobial biofilms have provided evidence of enhanced interspecies transfer of antimicrobial resistance traits, symbiotic interactions, and sequential colonization patterns. These observations raise the intriguing possibility that virulence traits associated with biofilm commensalism may be coselected through enhanced persistence and antimicrobial tolerance of such polymicrobial biofilms (20, 21).

### Native Tissue Infections

Although biofilm-related infections are most often associated with colonization of abiotic surfaces of IMDs, there is a growing body of evidence that biofilm colonization of natural surfaces may also be an obligatory component of some infections that involve no foreign body. These include urinary tract infections caused by uropathogenic *Escherichia coli* (22) and middle ear infections mediated by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, including chronic otitis media (23), as well as more persistent and chemotherapeutically challenging infections including chronic rhinosinusitis, cystic fibrosis mediated by *P. aeruginosa* (24), and native valve endocarditis caused by *Staphylococcus lugdunensis*, *Enterococcus durans*,

or Viridans group Streptococci. In such infections, antimicrobial therapy will continue to be driven by empiric observations. However, increasing acceptance of the potential role of biofilms in chronic infections with no known foreign body component, particularly those that fail to respond to conventional therapy, should promote studies to identify antimicrobial therapies with improved biofilm efficacy in these settings.

### Impact on Health Care Costs

The overall health care costs attributed to the treatment of biofilm-related infections have been systematically assessed in two recent reviews (6, 25). For infections of some uncomplicated nonsurgical IMDs (e.g., urinary catheters), the economic impact is quite low owing to the ease of implant extraction or replacement, although stress on the patient and the burden on the hospital staff are important considerations. Bacteremia resulting from CRBSIs in hemodialysis-dependent adults, however, is a much more serious problem, with a significant attributed cost (i.e., \$17,000 and \$32,000 for uncomplicated and complicated bacteremia, respectively) and a high probability of secondary complications including infective endocarditis, osteomyelitis, septic arthritis, septic emboli, and stroke (26, 27). Similarly, costs associated with infection of surgical implants range from \$15,000 per event for orthopedic fracture-fixation devices to more than \$50,000 to replace an infected mechanical heart valve (25). Clearly, we need new treatment options for the management of biofilm-associated infections that will simplify surgical practices and/or shorten typical hospital stay requirements.

### MECHANISMS UNDERLYING THE ANTIMICROBIAL TOLERANCE OF BIOFILMS

Inadequate exposure of antimicrobial agents at all relevant sites of infection is one of the principal factors underlying

chemotherapeutic failure and presumably limits the efficacy of some agents in deep-seated biofilm-associated infections. Assuming adequate exposure at sites of biofilm infections, subsequent trapping of antimicrobial agents in the exopolymeric matrix of biofilms is often cited as a universal mechanism underlying the insensitivity of biofilms to antimicrobial action. It is true that the penetration of experimental biofilms by some antibiotics, including vancomycin and ampicillin, is limited; however, other agents (e.g., tobramycin and ciprofloxacin, rifampin, and a variety of antifungal agents) exhibit good apparent diffusion through biofilms grown *in vitro*. In some cases, effective diffusion may be mediated by water-filled channels that are an architectural feature of biofilms. However, studies to assess the actual intracellular penetration of antimicrobials into cells within the biofilm matrix are lacking. Overall, the existing evidence does not suggest that exopolymeric matrix materials form a universal barrier that limits antimicrobial penetration to cells residing within a biofilm.

For bacteriostatic classes of antibiotics, which typically work in concert with host immune defenses, the location of bacteria within the exopolymeric coating of the biofilm structure is thought to effectively sequester cells from host immune cells and factors. This may in part explain their poor efficacy in this setting (28). However, no definitive studies have addressed whether there is a systematic difference between the efficacies of bacteriostatic and bactericidal agents in biofilm-associated infections *in vivo*. Interpretation of such a study would need to take into account differences in the exposure of different agents at the biofilm infection site(s).

The elevated expression of efflux pumps is another mechanism whereby cells can exhibit decreased susceptibility to antibiotics. The specific upregulation of genes encoding antibiotic transporters (or their regulators) has been observed in studies of biofilms formed by *Pseudomonas aeruginosa* (29), uropathogenic

*E. coli* (30), and *Candida albicans* (31, 32). However, studies of global changes in gene expression associated with biofilm adaptation suggest that upregulation of antibiotic transporters is not a universal theme. Of course, this mechanism is restricted to antimicrobial agents that are substrates for efflux transporters.

Adaptation to survival in the biofilm state requires changes in metabolic and catabolic pathways that can alter the intrinsic activity of antimicrobial agents in light of their mode of action (2). For example, experimental biofilms formed by CoNS are highly resistant to antibiotics that target cell wall biosynthesis while remaining susceptible to antibiotics that target RNA and protein synthesis (33). Such a response is consistent with a diminished role for cell wall biosynthesis in the biofilm population and reflects an ongoing role for transcription and translation in biofilm establishment, maturation, and propagation. It is interesting that so-called small colony variants (SCVs) of bacteria, characterized by a reduced *in vitro* growth rate owing to genotypic changes in metabolic pathways (34), have been isolated from both experimental biofilms and patients with persistent infections that are probably biofilm-associated. These include *P. aeruginosa* SCVs isolated from biofilms grown *in vitro* and from cystic fibrosis patients (35), an *E. coli* SCV isolated from a chronic prosthetic hip infection (36), and *S. aureus* SCVs from patients with cystic fibrosis, osteomyelitis, and device-related infections (37). Hence, genotypic adaptations that alter metabolic capacity and decrease growth rate may in some instances contribute to both antibiotic tolerance and the persistence of some biofilm-related infections.

Physiologic heterogeneity is another feature that distinguishes bacteria cultivated in a biofilm state from their planktonic counterparts. This phenomenon affects rates of growth and metabolism and is thought to reflect a combination of interbacterial quorum-sensing signals, accumulation of toxic byproducts, and dissimilar local microenvironments

(e.g., different nutrient or oxygen gradients) that arise in the three-dimensional biofilm community. Such phenotypic heterogeneity has been linked to the decreased susceptibility of a subset of cells in the biofilm to specific antimicrobials. These so-called persister cells are not resistant to the antimicrobial *per se* but instead appear to escape killing through what is hypothesized to be a transient dormant state (38). The molecular events that lead to the antibiotic tolerance of such persister variants are still poorly understood, but specific genetic loci have been identified that appear to affect their rate of formation.

In summary, although the antibiotic tolerance of both medical and experimental biofilms is a well-established phenotype, the molecular mechanisms that govern this phenomenon are complex and appear to vary across species, antibiotic classes, and settings.

## EXISTING THERAPIES

### Prophylaxis

Prophylactic use of antibiotics and microbicides can reduce the incidence of biofilm-associated infections of IMDs. Strategies for prophylaxis include device coatings, device immersion, surgical site irrigation, antibiotic-loaded cements, and antibiotic lock therapy. In the latter, a concentrated antibiotic solution is instilled into a catheter in a volume adequate to fill the lumen. The catheter is then “locked” into place for an extended period while the catheter is not in use, with the goal of preventing a line from becoming colonized and thereby reducing the risk of infection.

Although the use of antibiotic prophylaxis is controversial because of its potential to increase antimicrobial resistance, it is increasingly common in high-risk patient groups. With regard to device coatings, a recent and comprehensive meta-analysis of randomized controlled trials of rifampin-impregnated CVCs suggests they are both safe and effective in reducing the rate of catheter colonization and CRBSIs (39). Similarly, in six inde-

pendent studies of the efficacy of antibiotic lock therapy in the prevention of CRBSIs in hemodialysis patients, an overall reduction of 64%–100% in CRBSIs was apparent (40).

### Treatment: Surgical Intervention Combined with Antimicrobial Therapy

Replacement or removal of an infected IMD, combined with systemic antibiotic and/or antifungal therapy, is the most effective treatment in most settings. Standard practice involves either a one-stage or a two-stage procedure (25, 41, 42). For managing IMD infections in nonsurgery patients, long-term antimicrobial suppressive therapy remains the only option, and current salvage rates are highest with early diagnosis (43).

Recommendations of antibiotic therapies for the management of biofilm-associated infections have been driven largely by empiric observations and typically involve the use of combination regimens over extended periods (25, 41, 42). Recent reviews summarize current recommended practices for the treatment of infections of prosthetic joints (10, 41, 44), arterial prostheses (9), vascular catheters (45), prosthetic heart valves (46, 47), central nervous system shunts (48), pacemakers and defibrillators (49), endotracheal and tracheostomy tubes (50), and hemodialysis and peritoneal hardware (51), as well as treatment of FBIs of the urinary tract (52).

In most settings, the preferred treatment option(s) have arisen through cross-study comparisons of the cure rates or other clinical outcomes achieved for particular treatment courses. Relatively few clinical studies have directly compared alternate therapeutic-treatment regimens. In the clinical evaluation of antibiotic regimens, draft guidelines for the design and conduct of efficacy studies in the United States are available only for the CRBSI setting, and direct comparator studies have rarely been undertaken in any IMD infection setting. However, of all agents studied, the utility of rifampin combination therapies for

staphylococcal IMD infections has perhaps been most thoroughly evaluated in clinical trials. In these studies, rifampin was combined with quinolones (53–57), beta-lactams (53) or fusidic acid (58), and rifampin-containing regimens are now established as standard therapies for a range of device-associated infections (10, 11, 41, 43, 46, 48).

Fungal biofilm-associated infections are notoriously difficult to treat systemically with antifungal agents. This poor *in vivo* efficacy is not surprising, given the *in vitro* insensitivity of biofilms formed by *C. albicans* and other species to various classes of antifungal agents (13, 15, 16). However, agents of the echinocandin class exhibit significantly superior *in vitro* activity in killing fungal cells in established biofilms (14) and in suppressing biofilm colonization of materials (59). Echinocandins have also demonstrated activity in a rabbit model of an intravascular catheter infection (60). These activities may reflect a specialized role for glucan synthesis, the cellular pathway targeted by echinocandins, in the biofilm state or the resulting increased osmotic instability of echinocandin-treated cells. Lipid-based formulations of amphotericin B have also proven effective in *in vitro* assays of biofilm activity. The management of fungal biofilm-associated IMD infections involves exchange of the infected device, where possible, combined with systemic antifungal therapy (16). Data from *in vitro* studies and animal studies of biofilm efficacy, combined with the observed clinical success in management of disseminated candidiasis, suggest that antifungals of the echinocandin class (caspofungin, micafungin, anidafungin) and amphotericin B lipid formulations represent the best available options for the management of biofilm-associated infections with a known or suspected fungal involvement.

## EXPERIMENTAL THERAPIES AND FUTURE OUTLOOK

New experimental approaches for the management of biofilm-associated infections of

IMDs are listed in **Table 2**. These include a wide range of modified devices and surgical materials, most of which are intended for prophylaxis applications. They utilize new materials that resist colonization by microbial pathogens and novel device-coating approaches wherein antibiotics, microbicides, or quorum-sensing inhibitors are either covalently bound to the device or locally eluted from it. In the latter category are the so-called intelligent implants, which are designed to locally release agents when they detect microbial colonization (61). Finally, IMDs that emit low-energy surface acoustic waves (62), electric currents (63), or pulsed ultrasound (64) have been reported to either reduce device colonization or enhance the release and/or effectiveness of locally applied antibiotics. In addition to these device modifications, new studies have evaluated the effectiveness of new antibiotic or microbicide immersion practices with IMDs to suppress surgical-site infections.

**Table 3** lists new investigational and recently approved antibiotics that have been evaluated for antibiofilm activity through *in vitro* studies and/or animal models to assess their clinical potential in both prophylaxis and treatment. In the prophylaxis setting, agents of the lipopeptide and lipoglycopeptide classes show promise as potential new antibiotic lock therapies, which may reflect their common mechanistic feature as rapidly bactericidal agents (65). In the treatment setting, only dalbavancin has been evaluated in a specific human comparator trial, where it was found to exhibit efficacy superior to that of vancomycin in treating CRBSIs (66). In studies of refractory Gram-positive infections in orthopedic patients, quinupristin-dalfopristin (67) and linezolid (68) have been reported to have clinical cure rates of 78% and 55%, respectively, although long-term use of these agents has been associated with significant adverse events.

In light of the paucity of effective agents for the treatment of biofilm-associated infections, systematic studies have been undertaken to

**Table 2 Experimental approaches for the treatment or prophylaxis of biofilm-associated infections**

Approach	Mode of action	Key reference
pilicides	inhibits bacterial pilus biogenesis and surface attachment	71
RNA III inhibiting peptide (RIP)	disrupts quorum-sensing pathways in staphylococci	72
acyl-homoserine lactone mimetics	disrupts quorum-sensing pathways	73
furanones	disrupts quorum-sensing pathways	74
omigard (omiganan cationic peptide)	topical gel for prophylaxis settings including CRBSIs	<a href="http://www.cadencepharm.com">http://www.cadencepharm.com</a>
aganocides	hypochlorous acid-based compounds	<a href="http://www.novacal.com">http://www.novacal.com</a>
ceragenins	depolarizes membrane potential; device coatings	<a href="http://www.ceragenix.com">http://www.ceragenix.com</a>
lysostaphin	prevents or disrupts staphylococcal biofilms	<a href="http://www.biosynexus.com">http://www.biosynexus.com</a>
device coatings	controlled release of antimicrobials from device surfaces	<a href="http://www.surmodics.com">http://www.surmodics.com</a>
		<a href="http://www.bacterin.com">http://www.bacterin.com</a>
hydrogel coatings	controlled release of silver compounds	<a href="http://www.bardmedical.com">http://www.bardmedical.com</a>
surface acoustic waves	disrupts device adhesion and colonization	62
pulsed ultrasound	enhances local release of antibiotic from cements	64
electric direct current	prevents or disrupts biofilm colonization	63
intelligent implants	MEMS-based release of antimicrobial(s) from reservoir	61
gallium compounds	antimicrobial potentiator via disruption of iron metabolism	75

Abbreviations: CRBSI, catheter-related bloodstream infection; MEMS, microelectromechanical systems.

identify the most promising antibiotic combinations in both in vitro assays and animal models of biofilm efficacy (69). Of all agents tested, rifampin was again the most common constituent of combinations active against

staphylococcal biofilms, reflecting this agent's excellent efficacy against slow-growing and adherent staphylococci and its excellent tissue penetration. However, because of the significant resistance liability associated with

**Table 3 Biofilm-related activity of approved and investigational antimicrobial agents**

Antimicrobial	Description	Biofilm-related activity	Key reference
dalbavancin	lipoglycopeptide	CRBSI treatment	66
daptomycin	lipopeptide	biofilm reduction as lock solution in CVC model	65
		right-sided endocarditis	77
		poor in vitro activity on adherent staphylococci	78
linezolid	oxazolidinone	effective in combination with rifampin	76
quinupristin-dalfopristin	streptogramins	bone and joint infections	67
		biofilm reduction as lock solution in CVC model	79
telavancin	lipoglycopeptide	biofilm reduction in sorbarod model	80
tigecycline	glycylcycline	biofilm reduction in silicone disk model	76
		effective in combination with rifampin	81
CBR-2092	rifamycin-quinolone hybrid	optimized for biofilm activity	70

Abbreviations: CRBSI, catheter-related bloodstream infection; CVC, central venous catheter.

all approved or investigational rifamycins, these agents are limited to use in combination with an appropriate partner (11, 70). Most recently, a series of stable rifamycin-quinolone hybrid antibiotic agents have been reported (70) that were optimized for antimicrobial activity and resistance prevention properties against staphylococci in the biofilm setting.

## CONCLUSION

Microbial biofilms have gained recognition as the etiologic agents of many chronic and persistent infections of native tissues and IMDs. Owing in part to their adherent nature and slow growth, such infections are difficult to diagnose and treat with conventional approaches. As the use of IMDs increases, the incidence of biofilm-related infections represents a current and growing unmet medical need.

With current technologies and treatment options, prophylaxis to prevent or limit biofilm colonization of IMDs appears to be the single most effective approach. A number of national bodies have adopted more stringent barrier control policies to limit bacterial contamination of IMDs at the time of insertion. Routine use of antimicrobials in this setting remains controversial because compelling evidence of their effectiveness is lacking and their application is likely to further exacerbate the overall problem of antibiotic resistance in the nosocomial setting. Therefore, the prophylactic use of existing antibiotics for treatment of sys-

temic infections will probably continue to be discouraged.

In the immediate future, the application of noninvasive imaging technologies, combined with a wider recognition of the role of biofilms in IMD infections, is likely to lead to more rapid diagnosis of biofilm-related infections and consequent earlier adoption of the best available treatment options. For the longer term, systematic studies to discover or optimize antimicrobial agents that either exhibit improved killing of organisms in the biofilm state or potentiate the biofilm activity of existing antimicrobial agents hold promise. However, the existing regulatory climate does not provide a clear path toward the design and implementation of clinical trials to evaluate the efficacy of antibiotics (or antibiotic potentiators) in biofilm-related infection settings, and there is limited current evidence of the pursuit of this approach in the pharmaceutical industry. Industry efforts in this area may be encouraged by revision of the existing clinical study guidelines to address inclusion and exclusion criteria and efficacy endpoints for biofilm-related infections such as CRBSIs. With regard to efficacy endpoints, the use of biomarkers and/or advanced imaging technologies may be considered once they are appropriately validated in animal models of biofilm-related disease. Finally, a better understanding of host-pathogen relationships and further elucidation of basic biofilm biology may reveal new biomarkers with utility in diagnostic settings and new biofilm-specific targets amenable to chemotherapeutic or immune intervention approaches.

## DISCLOSURE STATEMENT

The authors are employees of Cumbre Pharmaceuticals Inc., which has a rifamycin-quinolone hybrid antibiotic agent (CBR-2092) in clinical development that is intended for the treatment of biofilm infections.

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## Errata

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