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Review

Recent Developments in Multifunctional Antimicrobial Surfaces and Applications toward Advanced Nitric Oxide-Based Biomaterials

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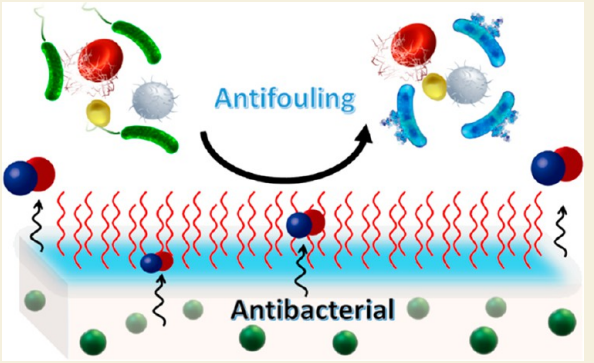
ABSTRACT: Implant-associated infections arising from biofilm development are known to have detrimental effects with compromised quality of life for the patients, implying a progressing issue in healthcare. It has been a struggle for more than 50 years for the biomaterials field to achieve long-term success of medical implants by discouraging bacterial and protein adhesion without adversely affecting the surrounding tissue and cell functions. However, the rate of infections associated with medical devices is continuously escalating because of the intricate nature of bacterial biofilms, antibiotic resistance, and the lack of ability of monofunctional antibacterial materials to prevent the colonization of bacteria on the device surface. For this reason, many current strategies are focused on the development of novel antibacterial surfaces with dual antimicrobial functionality. These surfaces are based on the combination of two components into one system that can eradicate attached bacteria (antibiotics, peptides, nitric oxide, ammonium salts, light, *etc.*) and also resist or release adhesion of bacteria (hydrophilic polymers, zwitterionic, antiadhesive, topography, bioinspired surfaces, *etc.*). This review aims to outline the progress made in the field of biomedical engineering and biomaterials for the development of multifunctional antibacterial biomedical devices. Additionally, principles for material design and fabrication are highlighted using characteristic examples, with a special focus on combinational nitric oxide-releasing biomedical interfaces. A brief perspective on future research directions for engineering of dual-function antibacterial surfaces is also presented.



KEYWORDS: *antibacterial, antifouling, biomedical devices, surface coatings, nitric oxide, biofilm*

1. INTRODUCTION

A large population in the world depends on biomedical devices such as stents, catheters, prosthetic joints and meshes, pacemakers, vascular grafts, endotracheal tubes, and orthopedic devices.[1−3] Although medical devices are beneficial to people with various types of diseases and health conditions, the proliferation of bacteria on the surfaces of these devices is a prevalent global problem.[4] Bacterial pathogens have become a severe threat by causing infectious diseases that lead to high morbidity and mortality worldwide and are the main cause of biomedical-device-associated infections such as catheter-related bloodstream infections (CRBSIs), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP) (Figure 1).[2,5] Approximately 687 000 people were affected by a hospital-acquired infection (HAI) in 2015.[6] More than 72 000 patient deaths were caused by HAIs in the United States, among which >25% were related to implanted medical devices.[7] Infections associated with medical implants often lead to postsurgical complications that require removal and replacement of the infected implant, leading to increased healthcare costs to patients and hospitals while increasing the rate of infection.[2] The widespread use of antibiotics has led to the prevalence of drug-resistant bacteria that are more dangerous and life-threatening because they are difficult to treat.[2] The most common pathogenic drug-resistant bacteria in biomedical-device-associated infections are methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), which account for a large number of healthcare-related infections per year, resulting in increased morbidity, higher risk of mortality, and a severe financial burden.[1] It was estimated by the O'Neill Commission that antimicrobial resistance will cost $100 trillion and over 10 million lives will be lost by 2050, making multidrug-resistant bacteria a major problem for the economy and public health.[5]

Biomedical-device-associated infections occur when planktonic bacterial cells attach to the surface of a biomedical device and form a multilayered biofilm from both Gram-positive and

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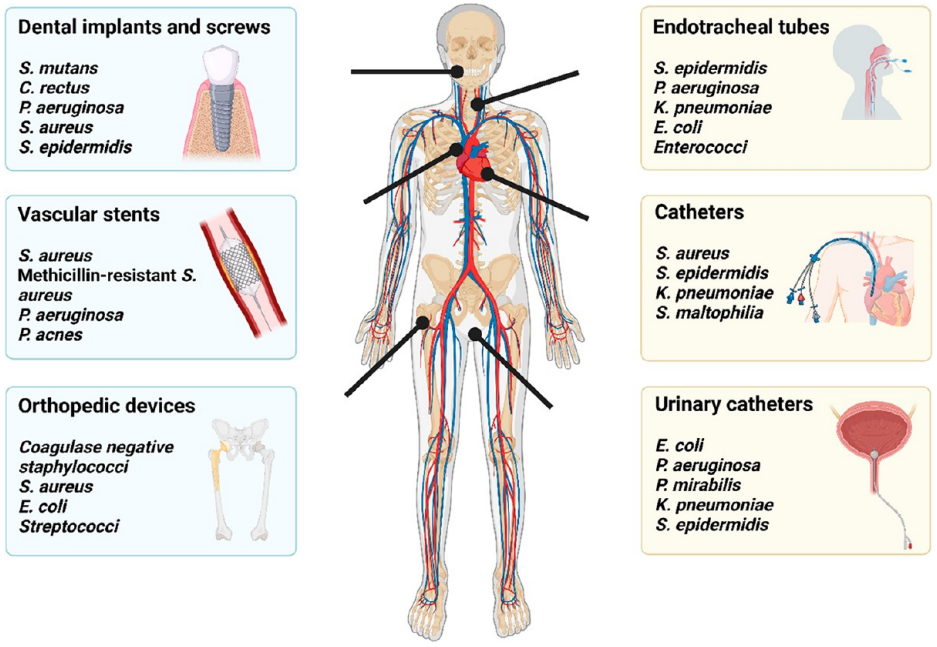

Figure 1. Examples of microbial species frequently responsible for causing biomedical-device-associated infections that arise from various implantable and indwelling medical devices. These include both short- and long-term devices, including dental implants, endotracheal tubes, vascular and peritoneal catheters, vascular stents, urinary catheters, and fracture fixation devices. The three most common infections arising from medical devices are catheter-related bloodstream infections (CRBSIs), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP). These are indicated by yellow boxes on the right.

Gram-negative bacteria including *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.[2,8,9] Biofilms are formed when planktonic bacteria adhere to an organic or inorganic surface and produce an extracellular polymeric substance (EPS) that is composed of proteins and other extracellular polymers (Figure 2A).[2] The formation of a biofilm can be considered as bacteria's defense mechanism to survive in a hostile setting and colonize new substrates. The bacteria protected within the EPS matrix largely vary in their genetic composition compared to free-floating planktonic bacteria, which makes them resistant to conventional antibiotic agents. These bacterial species deeply embedded in the biofilm require 1000 times higher dosages of antibiotics relative to free-floating planktonic cells, as not all antimicrobial agents can penetrate deeper into the matrix.[10] This high amount of drug increases the issues of antibiotic resistance in bacteria, leads to higher healthcare costs, and can be cytotoxic to other healthy cells or tissues.[11,12] Dental plaque, upper respiratory tract infections, peritonitis, and urogenital infections are examples of medical conditions that are associated with biofilms and often have an increased resistance to antimicrobial agents.[8] The interface between a medical device and the surrounding physiological environment (*e.g.*, urine, saline, blood, tissues, *etc.*) offers a suitable environment for the bacteria to attach and proliferate on the surface. The development of a biofilm on the surface of a medical device is heavily influenced by the physical characteristics of the device surface, such as surface roughness, hydrophobicity, surface charge, and bacterial membrane charge, which appear to govern bacterial adhesion and subsequent biofilm formation.[6,13] The complexity of biofilms increases with the presence of diverse microbial species, antibiotic-resistant genes, virulence factors, *etc.*, all of which make eradication of bacteria in biofilms a very challenging task.

Biofilm infections are difficult to eliminate because the EPS allows bacterial cells to proliferate while providing the necessary environment to protect bacterial colonies from immunological defense systems, nutrient limitations, and antibacterial agents.[2,4,14] Infections can then spread by detachment of bacterial cells from mature biofilms.[13] Furthermore, the accumulation of biofilms on a surface can impede the function, durability, and usability of medical devices and implants.[4,15] To solve these issues, significant attempts have been targeted toward creating antibacterial surfaces that can considerably lower the scope of preliminary microbial attachment and thus prevent the consequent biofilm development. These include generating bactericidal surfaces with an active killing mechanism or creating an antifouling interface for preventing bacterial adhesion on the device surface (Figure 2B).[16] Active antibacterial mechanisms kill bacteria on contact once the bacteria adhere to the surface. Polymers with an active mechanism are functionalized with cationic biocides, antimicrobial peptides, antibiotics, silver metal or nanoparticles, salts, or antimicrobial agents (see Table 1).[14,17] Quaternary ammonium compounds (QACs) are examples of active agents that have been investigated for antimicrobial coatings. These compounds disrupt the negatively charged bacterial cell surface, which leads to microbe death by exertion of strong electrostatic interactions with long cationic polymeric chains that penetrate the bacterial cell membrane.[3,18] Antimicrobial peptides (AMPs) exhibit antimicrobial properties that have been effective against both Gram-positive and Gram-negative bacteria, fungi, viruses, and unicellular protozoa; several AMPs can indirectly promote pathogen clearance by modulating the immune response of the host (Figure 2C).[19] The use of metal-based nanoparticles such as silver nanoparticles (AgNPs) has emerged as a strong approach for developing robust antibacterial surfaces.[20] The relatively smaller size of these particles along with a higher surface-to-volume ratio allows them to create a strong

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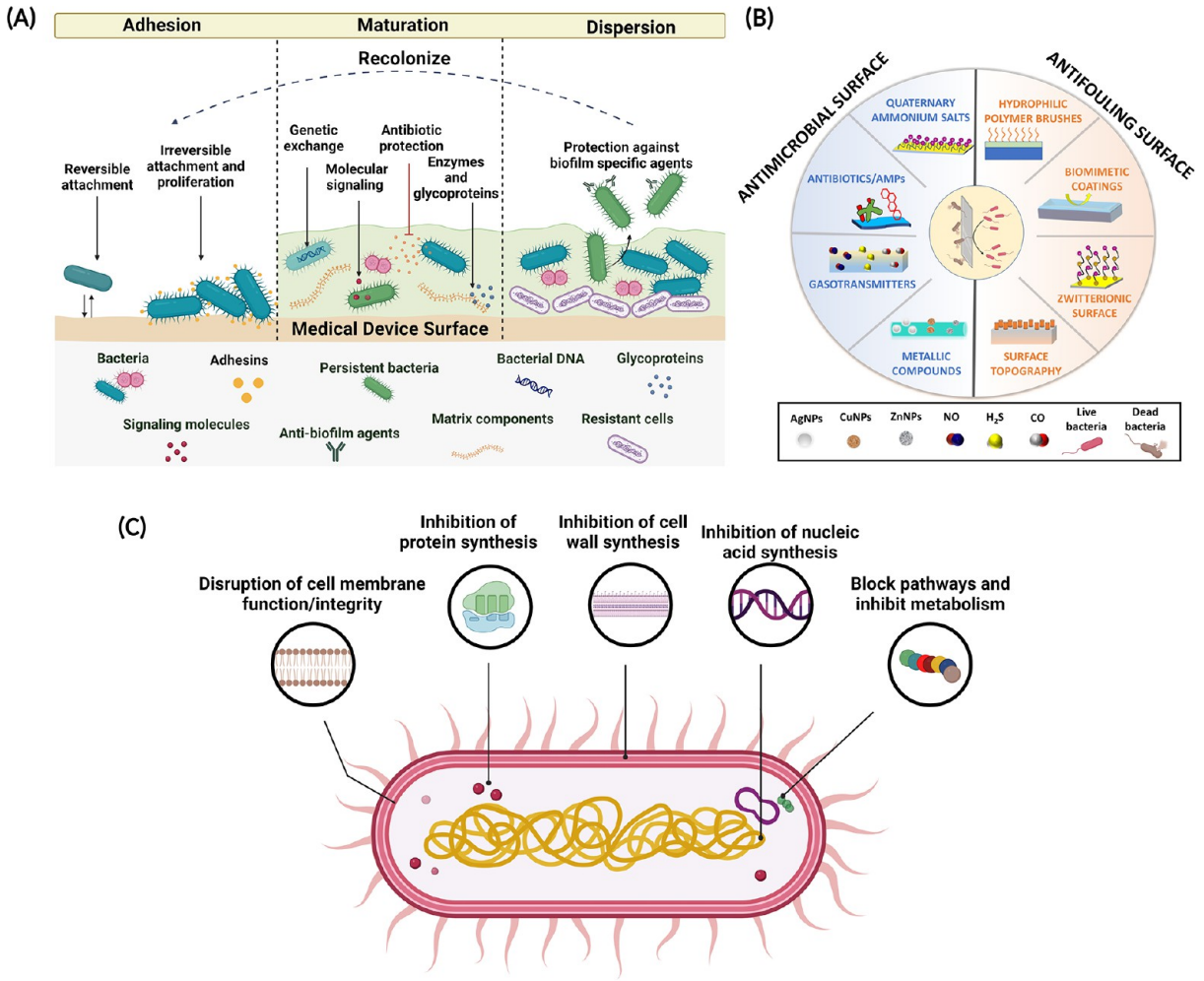

Figure 2. (A) Progression of biofilm formation and proliferation on a medical device surface. (B) Types of active and antifouling mechanisms used in the development of biomedical device surfaces. (C) The five common active killing mechanisms of antimicrobial biomaterials utilizing agents such as antibiotics, antimicrobial peptides, quaternary ammonium compounds, nitric oxide, and metallic nanoparticles to kill and eradicate bacteria on these surfaces.

interaction with the outer membrane resulting in significant antibacterial action. Materials with AgNPs exhibit nonspecific antibacterial activity, as there is no one specific receptor that these particles target. These characteristics make it more difficult for bacteria to develop resistance to the antibacterial mechanisms.[21] In contrast, antifouling coating materials such as poly(ethylene glycol) (PEG), poly(*N*-vinylpyrrolidone) (PVP), PEG-based copolymers, zwitterionic materials, and biomimetic materials such as polysaccharides, cell-membrane-mimicking strategies, slippery liquid-infused porous surfaces (SLIPs), and topographical patterns on the surface have been reported to reduce or inhibit biofouling by microbes on biomaterial interfaces (see Table 2).[17,22]

Polymers with an antifouling mechanism are generally hydrophilic or negatively charged or have a low surface free energy, which reduces protein adsorption and negates the hydrophobic and negatively charged properties of bacteria.[17] PEG is one of the commonly used antifouling materials, and it inhibits biofilm formation by resisting protein and polysaccharide adsorption on surfaces because of its high chain mobility, large exclusion volume, and the steric hindrance effect of the highly hydrated layer.[17,23] Zwitterionic materials, which are neutrally charged because they have equal amounts of positive and negative charge on the same molecule, are used for antifouling applications. Zwitterionic polymers can be formed with low-molecular-weight polymers that bind water molecules more strongly than PEG, resulting in a protective layer that increases the antifouling effect.[22,24] SLIPs are composed of U.S. Food and Drug Administration (FDA)-approved silicone oil to mimic the mucus production in the gastrointestinal tract and provide an ultralow-fouling surface that prevents protein adsorption and bacterial adhesion.[25] Topographical patterns with nano- and microstructures can obstruct the adhesion and interaction of bacteria in their collaborative work of developing EPS and biofilms on surfaces.

2. CHALLENGES WITH MONOFUNCTIONAL APPROACHES

Many reports have confirmed the limitations of exclusive antibacterial or antifouling coatings in hindering biofouling and biofilm formation. Adsorption of proteins, cells, or microorganisms on the surfaces of implanted biomedical devices poses a significant danger to human health.[24] Antifouling surfaces do not kill microorganisms but instead prevent adhesion through physical mechanisms.[26]

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Table 1. Classification of Single Antimicrobial Surfaces and Their Modes of Action

material classification	example compounds	mode of action
cationic biocides	quaternary ammonium compounds (QACs)	disruption of the microbial membrane through strong electrostatic interactions with the negatively charged bacterial cell surface
	chlorhexidine	disruption of the bacterial cell membrane by binding to the negatively charged cell wall and displacing the stabilizing calcium ions
antimicrobial enzymes	acylase	quorum quenching enzyme that cleaves the amide bond of acyl homoserine lactones
	lysozyme	hydrolytic enzyme that can catalyze the hydrolysis of β-(1−4) glycoside bonds between *N*-acetylmuramic acid and *N*-acetylglucosamine in the cell wall peptidoglycan layer
antimicrobial peptides (AMPs)	human β-defensin 3	formation of transmembrane pores and inhibition of cell wall formation and other essential parts of bacterial physiology
	LL-37	
	dermcidin	
antibiotics	β-lactams	disruption of peptidoglycan synthesis
	glycopeptides	inhibition of cell wall synthesis
	aminoglycosides	inhibition of protein synthesis through hydrogen-bonding interactions with the 16S rRNA of the 30S subunit
	quinilones	inhibition of DNA replication by inhibition of bacterial DNA gyrase
	sulfonamides and trimethoprim	inhibition of folic acid metabolism
metals	Ag ions	penetration of Ag ions into bacterial cells hinders DNA replication; Ag ions bind to proteins with the sulfhydryl group (−SH), which leads to a decrease/loss of enzyme activity
	silver nanoparticles (AgNPs)	AgNPs inhibit cell proliferation by causing oxidative stress to damage proteins and nucleic acids through the generation of reactive oxygen species (ROS)
	Cu ions	Generation of ROS makes Cu ions toxic to microbial cells
	copper nanoparticles (CuNPs)	CuNPs kill bacteria by forming stable complexes with vital enzymes inside the cell, which impedes cellular function
	zinc oxide nanoparticles (ZnONPs)	ZnONPs permeate into the cell membrane, which damages lipids, carbohydrates, proteins, and DNA through oxidative stress; vital cellular functions are disrupted by alteration of the cell membrane caused by lipid peroxidation
nitric oxide donors	*S*-nitroso-*N*-acetylpenicillamine (SNAP)	Highly reactive with superoxide radical to generate peroxynitrite, resulting in cellular oxidative stress; oxidation causes modification of protein functionality and DNA strands and damage to cell membranes; direct nitrosation of cysteine thiol groups in proteins by the NO radical can also readily alter the protein functionality and lead to cell stasis or death
	S-nitrosoglutathione (GSNO)	
	N-diazeniumdiolates	

Table 2. Classification of Single Antifouling Surfaces and Their Modes of Action

material classification	example compounds	mode of action
hydrophilic polymers	poly(ethylene glycol) (PEG)	large exclusion volume, chain flexibility, and steric hindrance of hydrated layer reduce protein and bacterial attachment
	poly(*N*-vinylpyrrolidone) (PVP)	low protein adsorption compared with PEG-modified surfaces
zwitterionic materials	zwitterionic polymers and polymer brushes	contain distinct chemical structures of anionic and cationic groups incorporated into the polymer structure that induce functionalities like antifouling abilities that can be controlled by adjusting the polymer charge density, pH sensitivity, and counterion association; zwitterionic polymer brushes have a strong water association ability that reduces nonspecific adsorption of protein, cells, and bacteria
biomimetic materials	polysaccharides	highly hydrophilic and able to form water-storing hydrogels with antifouling properties
	cell-membrane-inspired materials	form a structure that mimics the cell's outer membrane to prevent fouling
	slippery liquid-infused porous surfaces (SLIPs)	use capillary forces to reduce the surface adsorption and generate a low-adhesion interface between the material and contacting liquid
nano/micropatterned surfaces	nano/micropillars, square-shaped patterns	alter the total surface area and surface wetness of the substrate, affecting cellular signaling, cell membrane expression, and the function of bacterial flagella

Although antibacterial and antifouling mechanisms are effective methods to fight against infections, there are disadvantages to utilizing a single antibacterial or antifouling mechanism. Antifouling coatings can prevent bacterial adhesion on the surface up to a certain degree. However, they do not possess the ability to kill bacteria directly (Figure 3).[14,27] Functionalization of a surface with antifouling surface chemistry can also be compromised by the reactive physiological environment, leading to failure of the antifouling mechanisms (*e.g.*, patches of altered chemistry) where bacteria can begin attaching and forming a biofilm after prolonged implantation time. To date, not one surface has been reported that can attain 100% prevention of microbial infections in clinical applications.

While surfaces with active mechanisms can directly kill bacteria, they do not have the ability to release the dead bacteria and other bio-foulants accumulated on surfaces. In long-term applications, other live pathogens can use this debris as a substrate to colonize the surface, which can conceal the active moieties and reduce the efficacy of the device (Figure 3).[27] For example, the positively charged nature of QACs reduces antimicrobial efficacy by increasing protein adsorption and the accumulation of dead bacteria on the surface, blocking the influence of antibacterial compounds and leading to biofilm formation.[14] Cytotoxicity from high dose requirements, a narrow antimicrobial spectrum, and implications for propagating multidrug resistance are other potential drawbacks of compounds with a singular active mechanism.[14] Thus, with the

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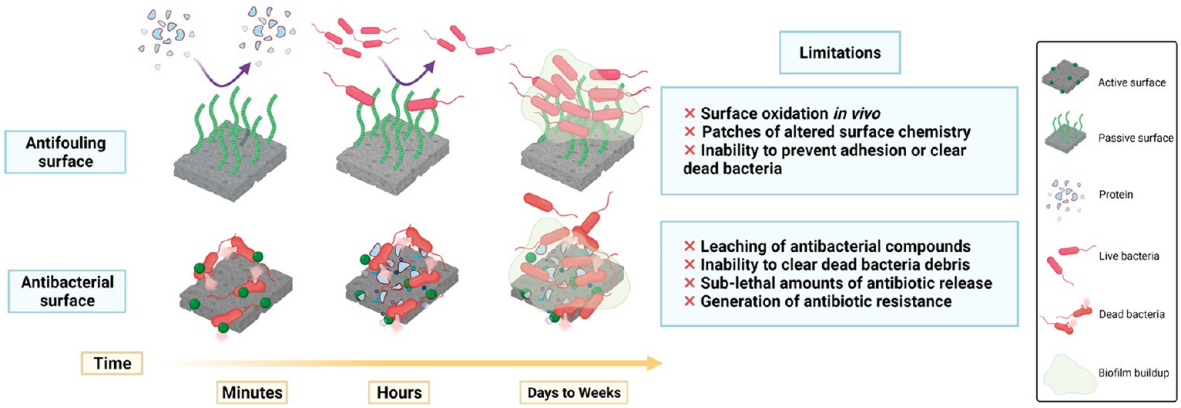

Figure 3. Progression of biofilm formation and proliferation on a medical device surface and failure of a singular approach to fully prevent infection on biomaterial surfaces. A passive surface can prevent or reduce the initial attachment of bacteria. However, the material chemistry can significantly change upon exposure to the physiological environment, which can lead to failure of the antifouling material chemistry. Ultimately, bacteria are able to breach the altered surface, colonize, and form a biofilm. Active surfaces with contact-based killing succumb to fouling from dead bacteria debris and proteins. However, the release of active agents from these biomaterials continues to eradicate pathogens until the source of the active agent becomes depleted. Both single-mechanism active and passive surfaces lead to eventual biofilm formation in long-term applications.

Table 3. Examples of Biomaterials with Antimicrobial and Antifouling Strategies

antibacterial component	antifouling component	target microorganism (s)	applications	ref
gentamicin	ethylene glycol linker	*S. aureus, E. coli*	titanium implant	49
sulfamethoxazole (SMZ) and trimethoprim (TMP)	PEG	*S. aureus, E. coli*	biomedical catheters	50
quaternized polyethylenimine	poly(glycidyl methacrylate) brushes	*S. aureus*	dental implant	119
poly(styrenesulfonate) (PSS), quaternary ammonium, H_2O_2 enzyme	zwitterionic novel copolymers (PTMAEMA-*co*-PSPE) with varied sulfobetaine fractions	*S. aureus* biofilm	urinary catheter	64
cationic antimicrobial polypeptides	heterofunctionalized PEG	*S. aureus, E. coli, P. aeruginosa*	surface coatings	120
rosin acid-derived maleopimaric acid quaternary ammonium cation (MPA-N^+)	allyloxy-PEG	*E. coli, S. aureus, P. aeruginosa*	biomedical device	14
chlorination of cysteine sulfurs	bovine serum albumin/zwitterion	*E. coli*	surface coating	84
silver, magnesium	pyrogallol	*S. aureus, S. epidermis, E. faecalis*, MRSA, *P. aeruginosa, E. coli, K. pneumoniae, A. baumannii*	suction catheters	121
α-aminoisobutyric acid	lysine	*E. coli, B. subtilis*	Foley catheters	122
vancomycin	phenylboronic acid polymer brushes	*S. aureus, S. epidermidis*	contact lens	123
silver	2-methacryloyloxyethyl phosphorylcholine	*E. coli, E. coli* K 1−2	catheters, stents, and dialysis equipment.	124
silver	perfluorodecanethiol	*S. aureus, E. coli*	catheters	125

great sense of necessity to produce a multi-functionalized material, integration of active surfaces having broad-spectrum antibacterial and antifouling functionalities have been widely reported.[28,29] Materials with the combination of multiple antibacterial mechanisms are expected to show synergy and provide a stronger combined defense against medical device infections.

Over the past few years, surfaces with multiple active components have been integrated into a single biomaterial interface using methods of tethering an active agent with a substrate embedded with an active antibacterial compound, two active antibacterial compounds embedded in the substrate, or light-sensitive compounds added to a conventional antibacterial agent. Many studies in the literature have reported approaches to combine dual active bactericidal surfaces that can help lower the microbial burden on medical devices. Such methods involve combinations of antimicrobial components such as QACs, metal (Cu, Zn, Ag) nanoparticles, antibiotic- and antimicrobial-coated/impregnated materials (chlorhexidine, silver sulfadiazine, rifampicin, gentamicin, *etc.*),[30−33] and nitric oxide (NO)-releasing therapeutic strategies.[34−37] Some of the materials with dual active strategies that involve a combination of two antibiotics have been successfully translated to preclinical stages.[31] For instance, indwelling catheters with chlorhexidine and silver sulfadiazine are commercially available and are at present used in patients to combat bacterial infections arising from biomedical devices. However, infections on medical devices are continuing to rise because (1) these surfaces lack antifouling mechanisms to prevent microbial adhesion and (2) the material surface is left vulnerable after the eventual depletion of the active antimicrobial agents over time.[38] Therefore, these limitations have motivated researchers to integrate antibacterial (bacteria-killing) and antifouling (bacteria/fouling-resistant) strategies into one substrate with broad-spectrum antimicrobial activity and mechanisms to discourage further bacterial adhesion and biofilm formation on the surface (see Table 3).

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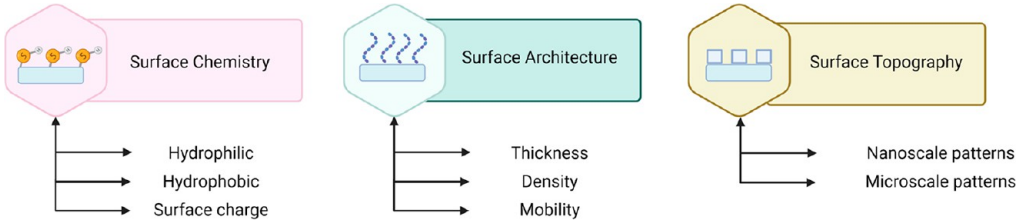

Figure 4. Three main surface modification techniques to create an antifouling interface on biomedical materials: surface chemistry, surface architecture, and surface topography.

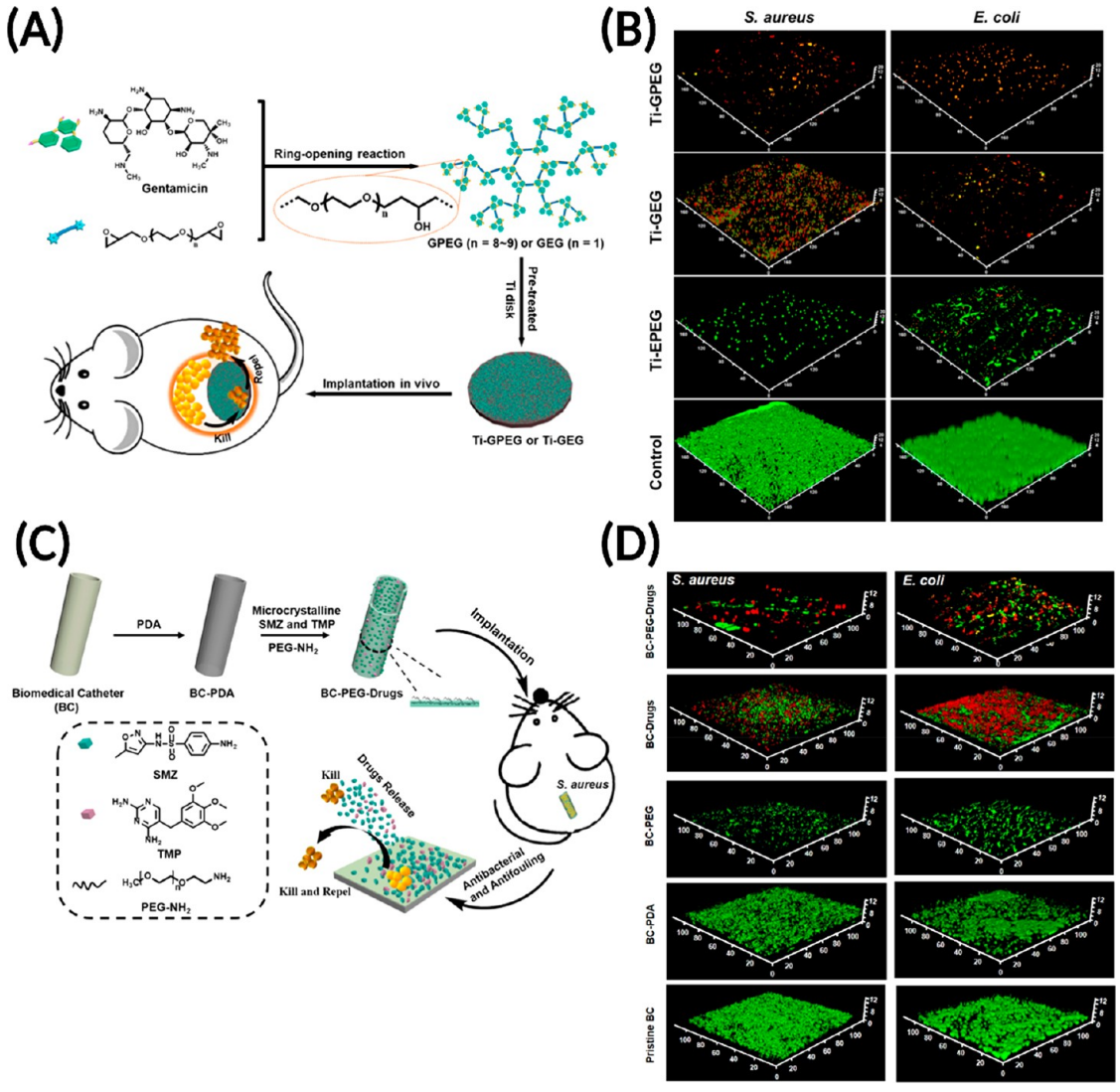

Figure 5. (A) Schematic representation of the synthesis and modification of a titanium implant surface to create an antifouling and antibacterial interface with gentamicin and poly(ethylene glycol) *via* a one-pot ring-opening reaction for *in vivo* applications. (B) These dual-functional modified surfaces (Ti-GPEG) show broad-spectrum synergistic antibacterial action against *S. aureus* and *E. coli* bacteria compared with unmodified and individual controls. Reproduced from ref 49. Copyright 2018 American Chemical Society. (C) Schematic representation of the generation of a dual-functional antibacterial surface with the microcrystalline antibacterial drugs sulfamethoxazole (SMZ) and trimethoprim (TMP) with PEG. (D) The surface-modified catheters showed significant antibiofilm and antifouling activity against *S. aureus* and *E. coli* bacteria after 7 days of incubation compared with individual and pristine controls. Reproduced from ref 50. Copyright 2019 American Chemical Society.

3. ANTIMICROBIAL SURFACES WITH DUAL ANTIBACTERIAL AND ANTIFOULING STRATEGY

3.1. Hydrophilic Polymer Brush-Based Coatings

To lower the bacterial attachment on the device surface, three important surface strategies have been extensively explored in the field of materials engineering to transform the hydrophilicity, hydrophobicity, and charge of the desired material (Figure 4). The other approaches include altering the surface topography through nano- and micropatterning and changing the surface architecture through the introduction of polymer brushes. These brushes can be tuned by adjusting the thickness, mobility, and density of the brushes on the surface. Chemical modification of

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surfaces with polymer brushes can enhance the antibacterial properties of materials. Hydrophilic cationic polymer brushes exhibit antifouling properties that influence the adhesion of microorganisms, proteins, and cells to a surface.[39−41] Employing antifouling polymer chains on a surface is a very valuable synthetic approach, as it enables widespread tuning of the surface properties merely by modifying the makeup, functionality, or structural design of the tethered polymer brushes. Regulating the surface-wetting properties, inhibition of nonspecific binding of biomolecules, colloidal stabilization, and resistance to fouling are all examples of successful application of polymer brushes. Notably, these polymer brushes can be functionalized on a range of materials with secondary antibacterial functions arising from antibiotics, nanoparticles, peptides, or zwitterion molecules to counteract implant-associated infections.[23,42−45] These surfaces are of particular significance because they can minimize the selection and propagation of resistant microbes, supporting persistent antibacterial efficacy.

Early studies on the development of dual-functional antimicrobial surfaces involved contact-active antibacterial and antifouling multifunctional coatings containing PEG with anchored antibiotics (penicillin, ampicillin, vancomycin).[46] These coatings could be easily applied on the surfaces of biomedical materials like poly(dimethylsiloxane) (PDMS), stainless steel, TiO_2, polytetrafluoroethylene (PTFE), and polypropylene (PP) using microwave plasma and chemical reactions to adjust the surface energy, roughness, and reactivity of the material surface.[47,48] Over the years, this phenomenon became more refined, allowing implant surfaces to be modified with hyperbranched polymers on a prefunctionalized surface and simultaneously linked to antibiotics. For example, a sequence of hyperbranched polymers comprising gentamicin moieties and PEG linkers was synthesized *via* a one-pot ring-opening reaction, namely, GPEG (from gentamicin and poly(ethylene glycol) diglycidyl ether) and GEG (from gentamicin and ethylene glycol diglycidyl ether) (Figure 5A).[49] Biomaterial interfaces such as Ti can be functionalized with hyperbranched polymers using polydopamine (PDA) adhesive chemistry. The antibacterial activities of the coated Ti disks (Ti-GEG, Ti-GPEG, Ti-EPEG (antifouling analogue)) were evaluated against *S. aureus* and *E. coli in vitro* and *in vivo* in a mice model, and a significant reduction in the number of viable cells adhered on the combinational implant surface (Ti-GPEG) was observed, demonstrating the excellent antibacterial and antifouling properties compared with the pristine and individual controls (Figure 5B). These characteristics of the dual-functionalized Ti disks presented potential clinical applications to reduce implant-related infections.

More recently, an efficient method for developing antibacterial and antifouling coatings on biomedical catheters (BCs) *via* codeposition of the microcrystalline antibacterial drugs sulfamethoxazole (SMZ) and trimethoprim (TMP) combined with PEG immobilization *via* PDA chemistry was reported (Figure 5C).[50] The products, termed BC-PEG-drugs, were effectively studied for their drug loading and releasing capacity in an acetic acid buffer solution (pH 5.5). The surface-modified catheters showed significant antibacterial and antifouling activity in solution as well as in the zone of inhibition study. Moreover, the drug-loaded coating along with PDA−PEG helped in inhibiting biofilm formation by *S. aureus* and *E. coli* for up to 7 days (Figure 5D) and showed exceptional antibacterial and antifouling abilities in an *in vivo* animal infection model against *S. aureus*. These drug-loaded implant coatings allow on-demand deployment of drug payloads and highlight the advancement of multimodal antibacterial remedies for clinical applications. Dual-function coatings of this kind illustrate great initial bacteria-killing efficacy due to the release of antibiotics and preserve significant antifouling activity after the depletion of embedded antibiotics because of the surface-immobilized polymer brushes.

However, antimicrobial materials that employ biocide release methods have demonstrated low accomplishment, with their primary disadvantage being the loss of activity as soon as the anti-infective molecules have been released or are no longer released at required dosages. Sublethal amounts of antibiotics have been shown to hasten resistance mechanisms and biofilm development.[51] Therefore, various innovative antimicrobial coatings that can supplant the high doses of traditional antibiotics have strongly influenced the field of surface chemistry. These coatings can be chemically altered to achieve a variety of features without altering the physical aspects of the base material. The fact that antimicrobial coatings can be readily applied to the surface of insertable or implantable medical devices underscores their importance in inhibiting bacterial adhesion, proliferation, and eventual destruction. In this regard, AgNP-based compounds have shown the potential to regulate bacterial contamination. However, safety concerns about the use of AgNPs have been raised because of their toxicity to mammalian cells.[52,53] The presence of AgNPs in the proximity of the cell membrane is reported to increase the amount of reactive oxygen species (ROS) to a toxic level. To address the issue of cytotoxicity, the antifouling properties of surface-immobilized PEG have been used to devise a defensive layer to protect against direct contact and uncontrolled release of AgNPs and Ag^+ ions from a material surface.[54] The literature suggests that at minimal concentrations such surfaces lack toxicity toward eukaryotic cells and interestingly are adequate to avert bacteria, including *E. coli*, *S. typhimurium*, *S. aureus*, and *S. pyogenes*.[55−58]

Another strategy is to develop a dual-function technology in which antibacterial gemini quaternary ammonium salt waterborne polyurethane (GWPU) brushes are placed over an antifouling layer of PEG and carboxyl anion of L-lysine.[59] The bactericidal activity of the upper layer at 4.96% biocidal concentration along with the antifouling features of the sublayer resulted in an augmentation of the coated surface which reduced the growth of both Gram-positive and Gram-negative bacteria by >99%. However, the long-term usage and *in vivo* applicability of coatings comprising hydrophilic moieties are restricted by the rich hydrophilic surface. Such polymers are prone to quicker release of the antibacterial component and are susceptible to disintegration by established biofilms in long-term *in vivo* applications. To improve the biocompatibility and stability of these materials, recently a cross-linked double-layer contact-active antibacterial and antifouling waterborne polyurethane was synthesized using PEG, L-lysine, and Gemini QAS (GQAS).[60] ATR-FTIR confirmed the stability of the cross-linked structure for at least 5 months with promising long-term antibacterial and antifouling applications. Moreover, these films exhibited >95% killing efficacy at 2 and 7 days after implantation, suggestive of great antibacterial action with diminishing acute inflammatory stage after 90 days of implantation *in vivo*. One major advantage of these release-based coatings is that the antibacterial moieties can not only kill the bacteria adhered to the surface but also eradicate the planktonic bacteria surrounding the medical device (*e.g.*, bacteria present in the

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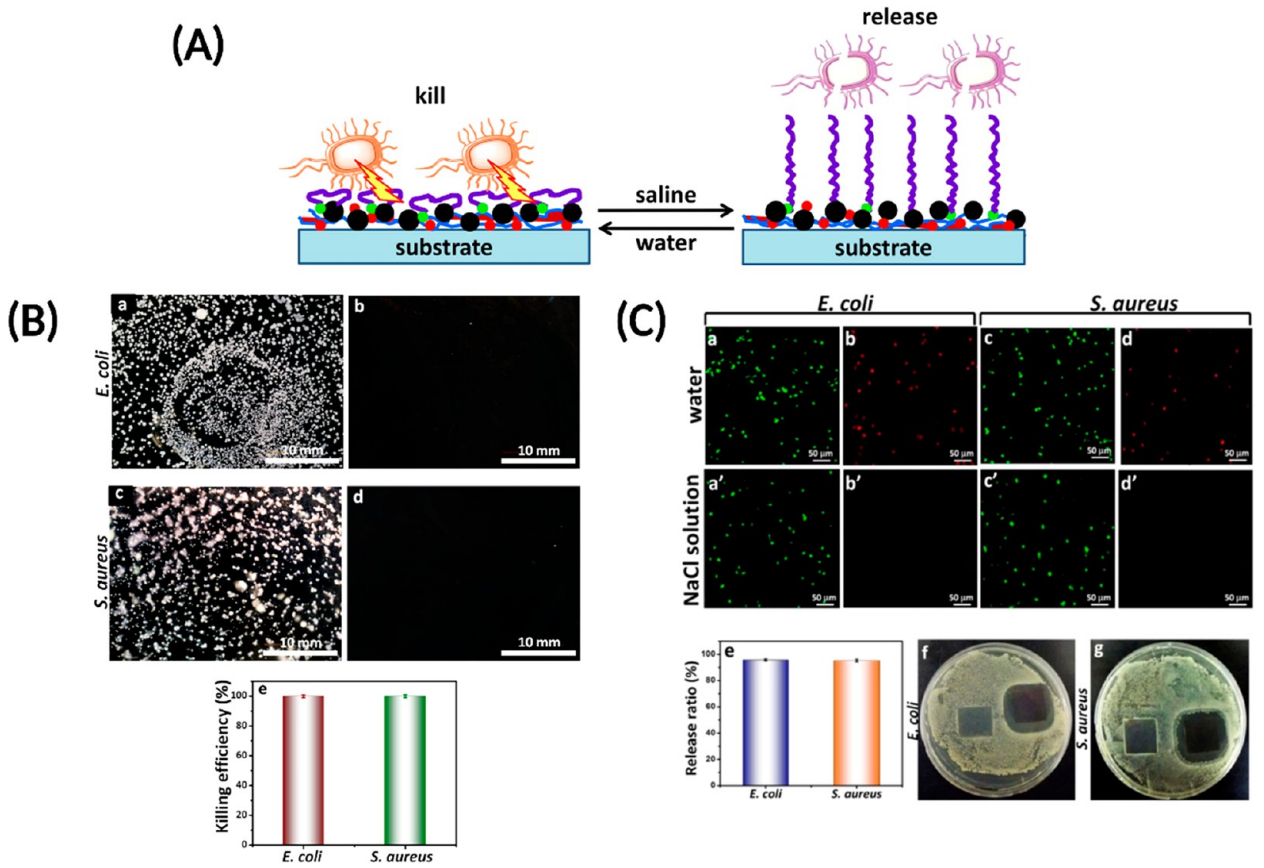

Figure 6. (A) Schematic representation of stimuli-responsive AgNP-conjugated polyzwitterion brushes on a polydopamine-functionalized substrate with dual-action bacteria-killing and -releasing properties. (B) (a–d) Images of (a, b) *E. coli* and (c, d) *S. aureus* bacteria on the surface of (a, c) control and (b, d) functionalized films. (e) Antibacterial efficacies of the surface-coated films against *E. coli* and *S. aureus*. (C) Representative live/dead images of *E. coli* and *S. aureus* bacteria on the modified surface upon the shift from water (a–d) to NaCl solution (a′–d′). (e) Release ratios of *E. coli* and *S. aureus* bacteria from functionalized surfaces upon transfer to NaCl solution. (f, g) Zones of inhibition of the modified surface *vs* bare Ti controls against *E. coli* and *S. aureus* bacteria. Reproduced with permission from ref 73. Copyright 2020 Elsevier B.V.

lumen of the catheter, saliva, or in the bloodstream) before their colonization on the surface. Dual-functional surfaces with bactericidal agent release have been explored with agents such as antimicrobial peptides,[44] antibiotics,[61] metallic nanoparticles,[62,63] enzymes,[64] *etc.* with on-demand release and switchable properties.

While PEG has been studied as a gold standard in antifouling materials, one challenge that has been observed is that it gets oxidized under physiological conditions, which results in the demolition of the hydration layer. Accordingly, efforts to find substitutes with higher stability have been directed toward an exploration of mixed polymer brushes, zwitterionic polymers, side chains, and surface grafts.[39,65] Neutral hydrophilic PEG alternatives, such as polyglycerol and poly(2-methyl-2-oxazoline), have demonstrated protein resistance comparable to that of PEG controls and improved oxidative stability on polydopamine-modified surfaces.[40,66−68] Bacterial species consist of negatively charged surfaces because of the presence of ionic carbohydrate, teichoic acid, and lipopolysaccharide structures. Therefore, antibacterial agents with positively charged surfaces composed of particles, polymers, and peptides have been developed and extensively investigated for their dual-functional antibacterial behavior against a vast span of bacteria, including multidrug-resistant strains.[69−71]

3.2. Zwitterion-Based Coatings

Many multifunctional antimicrobial surfaces in the literature have been fabricated through the incorporation of bactericidal agents into antifouling materials.[40,72] Materials with contact-based killing require the bacteria to adhere to the surface for efficient eradication of bacteria. However, the features offered by antifouling qualities restrict this process. To evade this conflict, the antibacterial and antifouling elements need to be spatially or chronologically distinct. To achieve this, PDMS-based silicone catheters with the ability to eradicate UTI pathogens were fabricated using electrostatic layer-by-layer assembly.[64] The coatings comprised three building blocks: a copolymer in conjunction with zwitterionic/quaternary ammonium side chains for antifouling properties; a derivative of the same polymer with octyl groups for potential bactericidal activity; and cellobiose dehydrogenase (CDH), another antibacterial moiety with H_2O_2-releasing capacity. The working of the integrated coatings was initially analyzed on silicon wafers as model substrates and later on the predeveloped silicone rubber surface following zeta potential, wettability, and morphological evaluation. The H_2O_2 byproduct of the immobilized CDH enzyme was the primary means of antibacterial activity from the surface-functionalized coating, which resulted in a >60% decline in viable *S. aureus* attachment. Moreover, the magnitude of the antifouling capacity of the coatings was observed to be reliant on the depth on the surface and remained stable for at least 10 days

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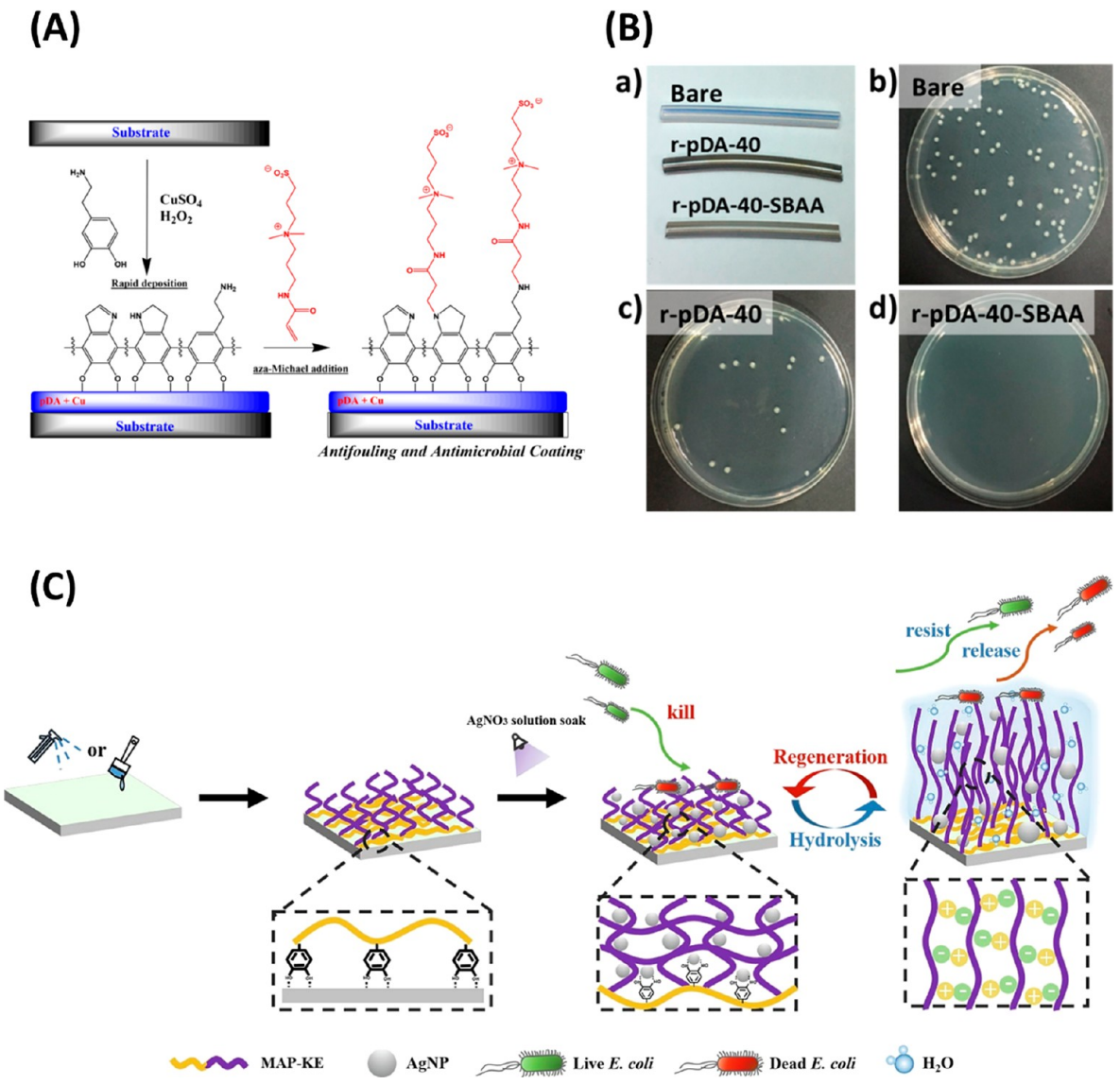

Figure 7. (A) Schematic representation of the formulation of a multifunctional antifouling and antimicrobial coating with PDA+Cu using aza-Michael addition on the surface. (B) (a) Optical images of silicone-based urinary catheters with and without surface modification. (b–d) Colonies were counted using a plate-counting method with *S. epidermidis* bacteria released from catheters (b) without modification or modification with (c) r-pDA-40 (d) and r-pDA-40-SBAA coatings. Reproduced from ref 87. Copyright 2018 American Chemical Society. (C) Schematic illustration of the fabrication of AgNP-loaded lysine and glutamic acid (Ag-MAP-KE) coatings with kill and release properties. In this approach, proteins are used as the base to reduce silver ions by the use of UV light and doped AgNPs. Reproduced with permission from ref 88. Copyright 2021 Elsevier B.V.

in water and urine. The controlled release of the antimicrobial moieties from functionalized surfaces can be utilized to lower microbial contamination on devices, prevent the attachment of free-floating bacteria, and inhibit biofilm formation.

Recently a novel zwitterionic monomer, 3-(dimethyl(4-vinylbenzyl)ammonio)butanesulfonate (DVBABS), and a polymeric coating that can both destroy bacterial cells and release the debris of dead cells from the device surface have been synthesized specifically for anti-biofilm activity.[73] These coatings were formulated *via* deposition of PDA following *in situ* synthesis of AgNPs and ultimately by grafting of polyDVBABS brushes using activators regenerated by electron transfer for atom-transfer radical polymerization (ARGET-ATRP). The PDA catechol groups immobilized the AgNPs, which resulted in the killing of bacterial cells, and a shift from water to a salt medium caused a reversible structural change of the polyzwitterion that resulted in the release of the bacterial cell from the surface (Figure 6A). For both *E. coli* and *S. aureus*, the multifunctional coating killed ≥99% of the attached bacteria (Figure 6B) and then quickly released ≥95% of the attached bacterial cells (Figure 6C). Both functions were found to be preserved over several cycles of killing and release.

A crucial antimicrobial mechanism of QACs requires the cationic chains to infiltrate the membrane of a bacterial cell.[74,75] This is achieved either by attraction of opposite charges and subsequent penetration of the active group leading to the disruption of the phospholipid bilayer or by establishing a charge imbalance that breaks down the transmembrane potential. The membranal integrity of the bacteria cell wall can be compromised upon transfer of cationic surface charges to active intrinsic cations in the membrane.[76] However, the positively charged QACs are more prone to intensifying the spontaneous protein adsorption in the *in vivo* setting, thus considerably reducing their antimicrobial ability.[77] Surface contamination by

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the debris from dead bacteria can conceal the functionalities on the modified surface containing QACs, which can increase the possibility of recurring biofilm growth.[78] To overcome this challenge, the antimicrobial activity of QACs has been integrated with the antifouling properties of hydrophilic polymers. On one hand, zwitterionic polymers can create robust and stable bonding with water molecules through electrostatic interactions, and on the other hand, hydrophilic polymers and coatings can help achieve surface hydration through the formation of hydrogen bonds between the polymer and water molecules. In addition to the surface hydration elements, zwitterionic polymers also tend to exhibit a strong anti-polyelectrolyte effect. In principle, the change in interactions of the polymer can lead to two diverse performances in water and salt solutions. Exposure to water and salt solution can lead to collapsed and stretched conformations of polymer brushes, respectively.[79] From an insightful perspective of composition and shape, the variations of cationic moieties and salt amounts and forms can be used to transform the surface wettability from a highly hydrophobic surface to a highly hydrophilic surface. Such a transformation in material properties has unveiled several research prospects involving the growth of multipronged bioresponsive materials that can revoke the shift between killing and releasing events (Figure 7).[80−82]

3.3. Surface Passivation *via* Protein Coatings

Additional antifouling strategies utilize specific protein interactions to prevent bacterial adhesion and nonspecific adsorption of other proteins. A classic example of this method involves the passivation of surfaces with proteins, which hinders cell attachment and blocks nonspecific protein adsorption. In order to reduce nonspecific interactions on polymers, various passivation agents are employed. Among these, bovine serum albumin (BSA) is most commonly used for surface passivation purposes because of its abundance, low fabrication cost, and lower degree of steric hindrance of specific binding proteins. Fabrication of stable protein films with BSA can be performed *via* nanoimprint lithography (NIL) to passivate surfaces.[83] This method comprises a blend of high temperature and pressure to generate materials that can substantially preserve the native structure of the protein under aqueous conditions. The coated surface can then be functionalized with various moieties such as chlorinating agents to produce *N*- or *S*-chloro species that would slowly release chlorine, providing a strong biocidal activity against uropathogens in addition to antifouling properties.[84] These protein coatings were also combined with nanoparticles as a nanobrick surface modification technique to create thin-film coatings on various substrates such as dental implant screws for biomedical applications.[85,86] Such robust approaches can be utilized toward scaling of medical device technology with protein films with an ability to be thermally treated to produce biostable coatings that retain their surface architecture (*i.e.*, hydrophilicity, biodegradability, surface charges, *etc.*) in an *in vivo* environment.

3.4. Surface Topography

Modifications of the surface structure *via* textured patterns have come out as an advanced method to hamper microbial adhesion, kill bacteria, or sensitize attached microbes on medical implants.[89] These surfaces are inspired by nature, where animal and plant surface topographies are employed to transform materials with bioinspired patterns for biofouling control. For example, surface characteristics like nanopillars or spikes have been shown to destroy the bacterial cell membrane, killing the bacteria and therefore obstructing bacterial adhesion.[90] Although the exact mechanism behind the bacteria repellence remains unclear, it is believed that nano- and microstructures radically reduce the contact adhesion area, generating improved bactericidal functions in comparison with smooth, solid surfaces. Single bacterial cells that encounter the textured surfaces undergo mechanical stress due to the patterns and lower surface area, which prevents them from attaching and results in significant distortions in the cell membrane, causing the membrane to rupture (Figure 8).[91,92] It is also understood

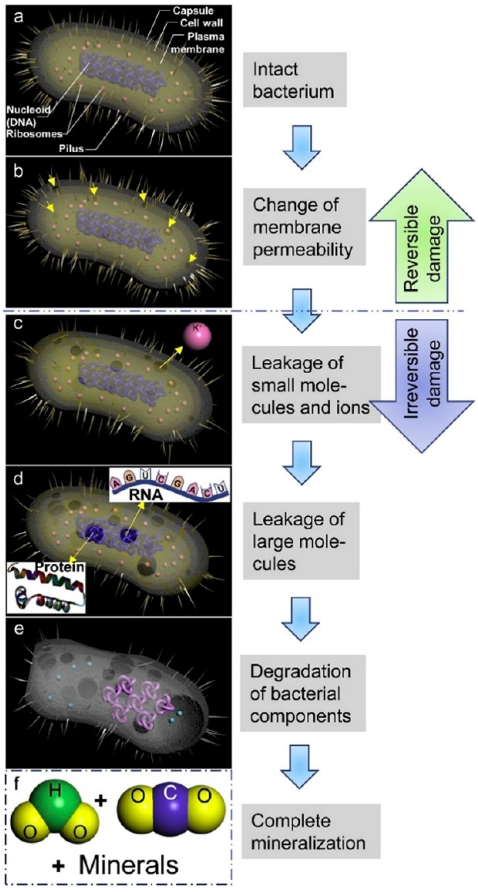

Figure 8. Schematic representation of photoinduced antibacterial process on a modified TiO_2 implant. (a) The process is initiated with attachment of bacteria to the surface with a rigid structure. (b) The pervasion of the bacteria cell membrane is influenced by the organic material oxidation force produced from the photocatalytic effect of TiO_2 (indicated by yellow arrows). (c) Further destruction occurs with increased perfusion of the cell wall and leakage of small molecules from the cytoplasm. (d) This process is followed by leakage of higher-molecular-weight elements (*e.g.*, nucleic acids and proteins) and (e) decomposition of internal constituents of bacteria. (f) Finally, the bacterial cell is fully mineralized to water, carbon dioxide, and nutrients. From ref 92. CC BY-NC-ND 4.0.

that surface patterns comprising nano/microstructures can disorder nanoscale domains in the bacterial membrane, a critical step of the biofilm development process.[93] Notably, bacteria can switch between planktonic and biofilm states by sensing the topographical patterns around them.[94] Thus, the presence of nano/microstructure on the surface can not only obstruct the adhesion of microorganisms but also prevent communication between bacteria in their collaborative aim of colonizing the surfaces. Studies have shown that patterns on the surface can

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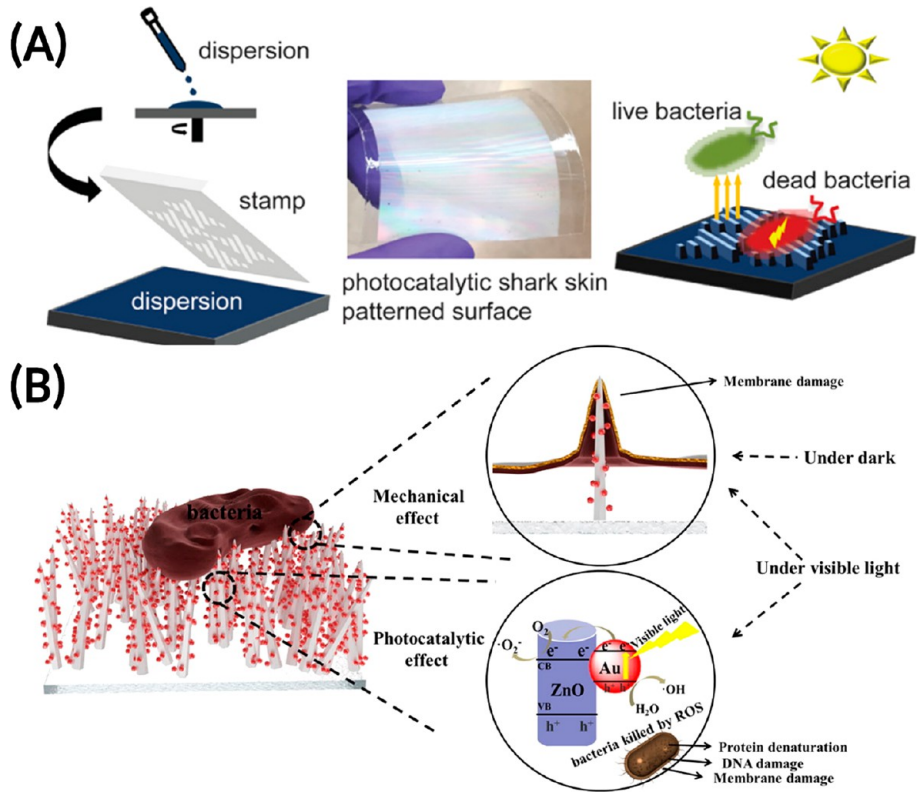

Figure 9. (A) Schematic illustration of shark-skin-inspired micropatterned surface topography integrated with TiO_2 NPs on a poly(ethylene terephthalate) (PET) substrate. Such surfaces can be produced *via* solvent-assisted soft nanoimprint lithography. Taking advantage of the photoirradiation properties of TiO_2 by incorporation of 10 wt % TiO_2 NPs into the chemical matrix enabled inactivation of >95% of *E. coli* and 80% of *S. aureus* within 1 h of UV light exposure. Reproduced from ref 107. Copyright 2018 American Chemical Society. (B) Dragonfly-wing-inspired patterned surface with bactericidal and antiadhesive properties comprising nanopillars made of zinc oxide (ZnO) and photocatalytic Au nanoparticles on a PDMS substrate. Reproduced with permission from ref 108. Copyright 2020 Elsevier B.V.

hinder flagellar interaction between bacteria and block the release and sensing of small signaling molecules that are responsible for EPS production and biofilm formation.[93]

It is worth noting that bacterial attachment to medical devices and materials is often generalized since bacteria are viewed as immobile, extremely soft, and geometrically defined particles. In reality, bacterial cells are extremely dynamic with a convoluted living system that alters the protein structure in the cell envelope on the basis of the surrounding physiochemical circumstances, affecting functions like protein secretion, EPS generation, extension of flagella, and adhesive molecules such as fimbriae.[95] Moreover, the bacterial form, size, growth conditions, and nutrient availability can all influence their interaction with the medical device interface. Therefore, there is no universal set system in terms of the topography of the surface that can prevent all microorganisms from adhering to the surface. Even though the implant at first may be inhospitable for bacterial adhesion, the buildup of a protein-rich conditioning film will ultimately initiate microbial adhesion and biofilm creation. Therefore, these patterned surfaces are primarily effective in delaying the early stage of bacterial biofilm growth when the number of cells is relatively low.[96] As the microbes start to grow and multiply, after a certain period, microorganisms will colonize the surface and initiate biofilm development. However, an ideal biomedical implant should possess the ability to not only delay but also completely prevent the growth of biofilms and associated infections. For this reason, microtopography alone is inadequate, and there is a need to develop multifunctional coatings that are both antifouling and antibacterial.

Polymers are widely used in a variety of biomedical applications, including short- or long-term-indwelling medical devices and implants. By their range of properties, today's polymer-based medical devices are formulated to provide excellent biocompatibility, durability, elevated potency, high-level wear endurance, and processing versatility over a wide range of applications. However, their applications are restricted by a lack of resistance mechanisms against biofouling and infections. Materials like poly(methyl methacrylate) (PMMA), poly(ethylene terephthalate) (PET), polyurethane (PU), PDMS, titanium, stainless steel, *etc.*, which are widely used in fabricating medical devices such as prosthetic devices, nasoenteral tubes, contact lenses, indwelling catheters, or orthopedic and dental implants, can be functionalized with nanopatterned structures using photolithography, etching, chemical vapor deposition, electrodeposition, nanoimprinting, and other texturing techniques.[97−99] By means of direct laser interference patterning (DLIP), periodic bacteria-repellent microstructures have been produced on a variety of metallic and non-metallic biomedical surfaces with antimicrobial agents.[100] It has been shown that pattern sizes similar to bacterial cell size (1−2 μm) thwart biofilm formation drastically by isolating the bacterial cells and successively lowering the microbial attachment.[101,102] This hypothesis has been used by several authors to sensitize and eradicate biofilms of *S. aureus* and *P. aeruginosa* with the synergism between micropatterned surfaces and streptomycin antibiotic treatment in the concentration range of 1−4 mg/L.[103] The bacteria-size surface topographic characteristics decrease bacterial adhesion and

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obstruct the growth of two-dimensional accumulations for the initial few hours.

Recent studies have largely reported the synergistic antibacterial effect of topographical cues and chemical components.[104,105] The combined effect of chemically modified surface and topography is known to have a greater impact on the adhesion and viability of *P. aeruginosa*.[106] The study consisted of a conducting polymer, polyaniline (PANI), and modification of the surface of PET by *in situ* polymerization and microstructuring of the surface using DLIP. The PANI-modified hydrophilic films decreased the attachment of *P. aeruginosa* by 74% and consecutive biofilm formation by 50%. The presence of microstructure and PANI on the dual-functional PET−PANI film further increased the ability to inhibit bacteria and biofilm formation by 97% and 65%, respectively. Similarly, the antimicrobial properties of inorganic surfaces like copper can be additionally boosted by directed surface functionalization using the same patterning technique.[100] However, one drawback of DLIP is that it can induce undesirable chemical variations in the surface of the polymer.[101] Therefore, the validity of the method for use in polymeric medical devices is still uncertain. Scientists have taken great inspiration from naturally occurring micro- and nano-topographies with high surface contact to modify biomedical materials that mimic these intricate architectures for their antibacterial and antifouling properties. Patterned structures often found on the cicada, dragonfly wings, shark skin, lotus, and rose petals or even liquid-infused surfaces possess the ability to inhibit or destroy bacteria.[109,110]

Evaluation of these surfaces illustrates extensive variants in elemental and conformational traits, suggesting that there is no one specific surface structure that demonstrates bactericidal performance against all types of microorganisms. Nevertheless, complex biological interactions between adsorption and release of protein moieties, cells, and microorganisms on the device interface may be dictated by these designs. For this purpose, high-performance dual-functional coatings that can repel and inactivate bacteria with UV-cross-linkable adhesive material based on shark-skin nanotopography have been developed.[107] This material was loaded with TiO_2 NPs from which shark-skin microstructures can be imprinted on a PET substrate using solvent-assisted soft nanoimprint lithography. Upon exposure to UV light, irradiated TiO_2 NPs produce reactive hydroxyl radicals and superoxide ions that can inactivate a variety of microorganisms.[111] The light-activated shark-skin-designed surfaces decreased the attachment of *E. coli* by ∼70% compared with smooth surface films with identical chemical compositions. Even the lowest tested concentration of 10 wt % TiO_2 NPs demonstrated >80% and 95% inactivation of *E. coli* and *S. aureus* within 1 h of UV light exposure (Figure 9A). The use of TiO_2 offers superior attributes for biomedical applications compared with other nanoparticles (*e.g.*, Ag, Cu) because of its ability to be loaded into transparent materials and device coatings.[112] This can be beneficial for many medical devices, such as blood-contacting devices, where early visual detection of blood clots is imperative.

As per the recent molecular dynamics model report, there is a strong correlation between bacterial adhesion, the physicochemical surface properties, and the design of a medical device, where both the device and bacteria determine the success of the device in terms of antibacterial activity.[91] Some structures like nanopillars found on surfaces of cicada and dragonfly wings can impede only certain types of bacterial strains.[113,114] The bactericidal efficacy of the surface is influenced not only by the shape, width, height, and spacing of the structural patterns but also by the cell type and rigidity of the bacterial cell membrane. This might be the reason why rigid Gram-positive bacteria strains, including *S. aureus*, are resistant to nanopatterned surfaces of cicada wings, while Gram-negative ones may not be affected to a similar extent.[115] To conquer this limitation, engineered surfaces with topographical patterns can be combined with antimicrobial compounds. In this regard, fluorine-loaded hydroxyapatite (FHA) has been widely employed with biomimetic structures for orthopedic and dental applications because of its broad-spectrum antibacterial efficacy against bacteria like *S. aureus*, *E. coli*, and *P. gingivalis*.[116] On the same basis, an integrated surface of cicada-wing-like nanopillars (diameter ∼ 80 nm) in conjunction with FHA on a titanium substrate using electrochemical additive manufacturing for biomedical applications has been designed.[117] Similarly, dragonfly-wing-based nanopillars made of ZnO/Au on a PDMS (PDMS-ZnO/Au) surface with dual bactericidal and anti-biofouling activity to reduce biofilm formation over a prolonged time have been reported (Figure 9B).[108] The superhydrophobic surface of modified PDMS with the ZnO nanopillars produces air pockets for a photocatalytic reaction that is enhanced with the addition of AuNPs. The antiadhesive and antibacterial PDMS-ZnO/Au surface demonstrated >99% bacteria reduction with just 30 min of visible light exposure, which can be attributed to ROS generation through photocatalytic reduction of AuNPs that results in membrane, protein, and DNA destruction in bacteria.[118]

4. ADVANCEMENTS IN NITRIC OXIDE-RELEASING MULTIFUNCTIONAL BIOMEDICAL DEVICES

Conventional approaches for tackling infections associated with medical devices using antibiotic treatments have exhibited decreasing effectiveness as complications with biofilms and resistant bacteria at the material interface become more prevalent. Moreover, these devices can often be affected by other biomedical issues, such as device-induced thrombosis and inflammation. It is understood that local and systemic microbial infections elevate the threat of thrombosis as much as 20 times and lead to thromboembolic diseases.[126] One main issue that underlines the risk of thrombosis is the degree of inflammation that is triggered by the occurrence of infection, in which a procoagulant state can increase inflammation and thrombotic complications.[127] The active antimicrobial surface strategies discussed in the previous sections, including antibiotics, metal nanoparticles, and QACs, can all effectively tackle bacterial contamination; however, they cannot address other biomedical challenges that occur at biomaterial interfaces (*e.g.*, thrombosis and inflammation). The use of materials that release nitric oxide (NO) has become a popular strategy to simultaneously overcome the issues arising from the use of biomedical devices, including the issue of biofilms.[128−132] NO is a diatomic free radical, gaseous transmitter molecule that is endogenously produced in the body when L-arginine undergoes enzymatic oxidation in the presence of nitric oxide synthase (NOS), resulting in the production of NO and L-citrulline.[133,134] Healthy endothelial cells generate a NO flux of $(0.5−4) \times 10^{-10}$ mol cm^{-2} min^{-1} in the blood vessels that protects against platelet activation and aggregation, exhibits an antiproliferative effect on smooth muscle cells (SMCs), and controls vasodilation and blood pressure.[135] Nitric oxide is known to regulate many physiological functions such as neurotransmission, vasodilation, immune response to infection, wound healing, angiogenesis, and

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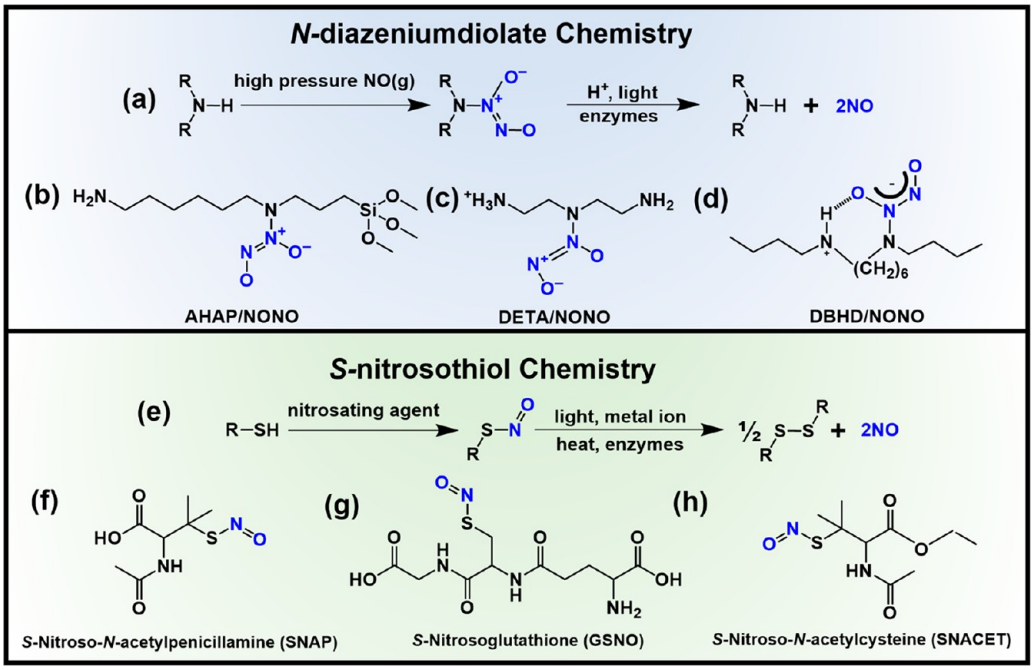

Figure 10. (top) *N*-Diazeniumdiolate (NONOate) chemistry: (a) schematic representation of the formation and decomposition of NONOates and (b–d) chemical structures of the NONOate donors (b) diazeniumdiolated *N*-(6-aminohexyl)aminopropyltrimethoxysilane (AHAP/NONOate), (c) diazeniumdiolated diethylenetriamine (DETA/NONOate), and (d) diazeniumdiolated dibutylhexanediamine (DBHD/NONOate) (bottom) *S*-Nitrosothiol (RSNO) chemistry: (e) schematic representation of the formation and decomposition of RSNOs and (f–h) structures of common NO donors (f) *S*-nitroso-*N*-acetylpenicillamine (SNAP), (g) *S*-nitrosoglutathione (GSNO), and (h) *S*-nitroso-*N*-acetylcysteine ethyl ester (SNACET).

oxygen-free radical generation.[136,137] Apart from these versatile properties, NO has also been found to possess excellent antimicrobial/bactericidal activity against both Gram-positive and Gram-negative bacteria, including several clinically resistant bacteria strains such as methicillin-resistant *S. aureus* (MRSA).[138−140] The antibacterial activity of NO is governed by multiple mechanisms such as nitrosation of amines and thiols, chemical alteration of DNA, lipid peroxidation, promotion of iron depletion in bacteria, and tyrosine nitration.[141−143] Moreover, NO has a very short half-life in the physiological environment, which makes its action very rapid, and as a result, bacteria are unable to develop resistance against NO.[144,145] These properties of NO make it a superior therapeutic compared with traditional antibiotics or other active antimicrobial agents discussed above.

The multifunctional antimicrobial, antithrombotic, and anti-inflammatory properties of NO make it a promising candidate for the development of various indwelling and blood-contacting biomedical devices with enhanced hemocompatibility and antimicrobial activity. The instability and short biological half-life of NO under aqueous conditions have led to the development of a pharmacologically active class of NO donors, such as nitrates, *N*-diazeniumdiolates (NONOates), and *S*-nitrosothiols (RSNOs), which can be integrated within a variety of medical-grade polymeric devices for prolonged and controlled NO release.[146−150]

NONOates are among the most widely studied NO-donating molecules. They are synthesized by reacting primary or secondary amines with NO in a very high pressure (*e.g.*, 5 atm) and low-temperature environment under basic conditions (Figure 10a–d). The release of NO from these compounds can be triggered by modulating the pH, light, or enzymes where 2 mol of NO is released per 1 mol of the donor.[151−153] RSNOs, another class of commonly investigated NO donating compounds, are endogenously found in the body and can be synthesized by conventional nitrosation of thiol functional groups in an acidic environment.[154,155] RSNOs can rapidly release NO under physiological conditions in the presence of various catalysts such as heat, light, metal ions, and enzymes (Figure 10e). *S*-Nitroso-*N*-acetylpenicillamine (SNAP) and *S*-nitrosoglutathione (GSNO) are two commonly used NO donor species that have been studied for biomaterial applications because of their long-term stability and NO release properties in addition to ease of synthesis, low cost, and excellent biocompatibility (Figure 10f,g).[156] Other RSNOs such as *S*-nitroso-*N*-acetylcysteine (SNACET) (Figure 10h) and derivatized molecules such as *N*-acetyl-*S*-nitrosopenicillaminyl)-*S*-nitrosopenicillamine (SNAP-SNAP) have also been synthesized and reported.[157,158] NO donors can be incorporated into a polymer matrix *via* solvent impregnation, non-covalent dispersion, blending of the donor in a polymer, or by covalent immobilization of the NO donor moiety to the polymer backbone (Figure 11).

NO-releasing materials have historically faced the challenges of attaining controlled NO release and long-term release properties to meet the requirements for various medical device applications. This is one of the challenges that has restricted effective clinical translation of NO-releasing materials to date. Because the therapeutic levels of NO and its effects can vary significantly under physiological conditions, it is essential to regulate the level of NO for the desired biomedical application. For example, during the introduction of a medical device implant to the body, the device may need elevated levels of NO to thwart the initial bacterial attachment on the device surface. Nevertheless, over longer durations, these implanted devices may need reduced levels of NO to maintain a bacteria-free state. NO release from materials has been determined by a combination of the NO donor chemistry and the material

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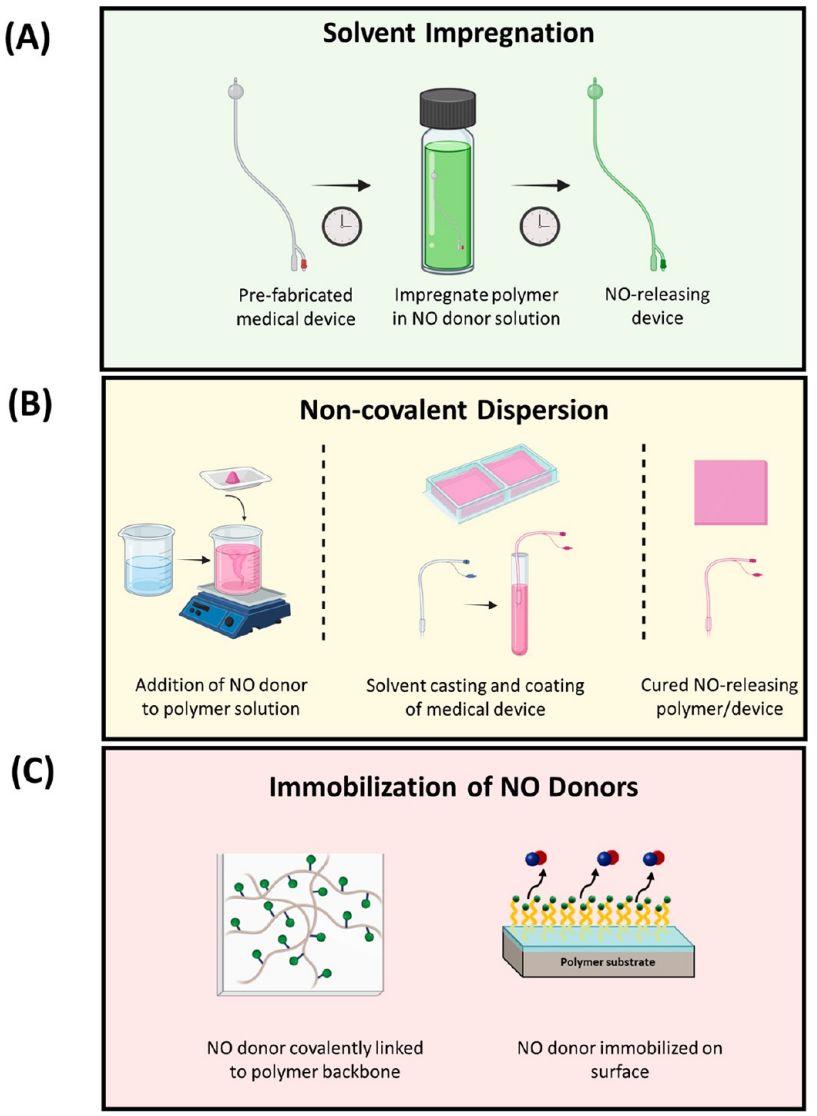

Figure 11. Methods to generate NO-releasing/generating materials: (A) solvent impregnation, (B) non-covalent dispersion of NO donors in a polymer solution and solvent casting, and (C) immobilization of NO donors on a functionalized polymer substrate.

properties. Recent work has utilized approaches that can control the NO release by modulation of the polymer properties (water uptake), dip coating with a hydrophilic polymer to create a hydration layer and prevent adsorption of biomolecules, coating with a low-water-uptake/hydrophobic polymer, covalent immobilization of NO donors that can control leaching and prolong NO release, or elevation of the NO level using catalysts (light, metals, enzymes, *etc.*).[159−161] The metal-based catalysts can also provide a second active antimicrobial mechanism while helping control the NO release. Similarly, to precisely regulate the dosage and NO delivery time from polymers, the photoresponsive properties of NO donors have been exploited for various biomedical applications (catheter disinfection, NO inhalation therapy, osteosarcoma therapy, *etc.*).[153,161−163] Another approach for controlling the location and enabling site-specific NO availability is the use of transnitrosation reactions at thiol moieties (*e.g.*, cysteine) that are immobilized on surfaces to provide localized sites for NO at these biointerfaces.[164−167] The specific details of these combinational materials are discussed later in this review.

4.1. NO-Releasing Combinational Surfaces with Dual Antimicrobial Strategies

The use of NO-releasing antimicrobial surfaces is a promising approach to increase the lifetime and enhance the biocompatibility of medical devices. Nevertheless, one major issue with these devices is that the levels of NO may decline with time because of degradation of the NO donor within the polymer matrix, which restricts the potential of devices to eliminate bacteria over longer durations. Therefore, many efforts in the field have been directed toward combining dual-active antimicrobial approaches (Figure 12). These strategies are exciting since medical devices with NO and a secondary antimicrobial mechanism will not only help with tackling infection issues at medical device interfaces but also help overcome other significant challenges with indwelling medical devices such as thrombosis, inflammation, *etc.* because of the inherent biological properties of NO.

Surface modifications of NO-releasing antibacterial polymer coatings are attempted to bestow additional antibacterial properties to synergistically combat bacteria. These techniques involve incorporation of the NO donor along with secondary

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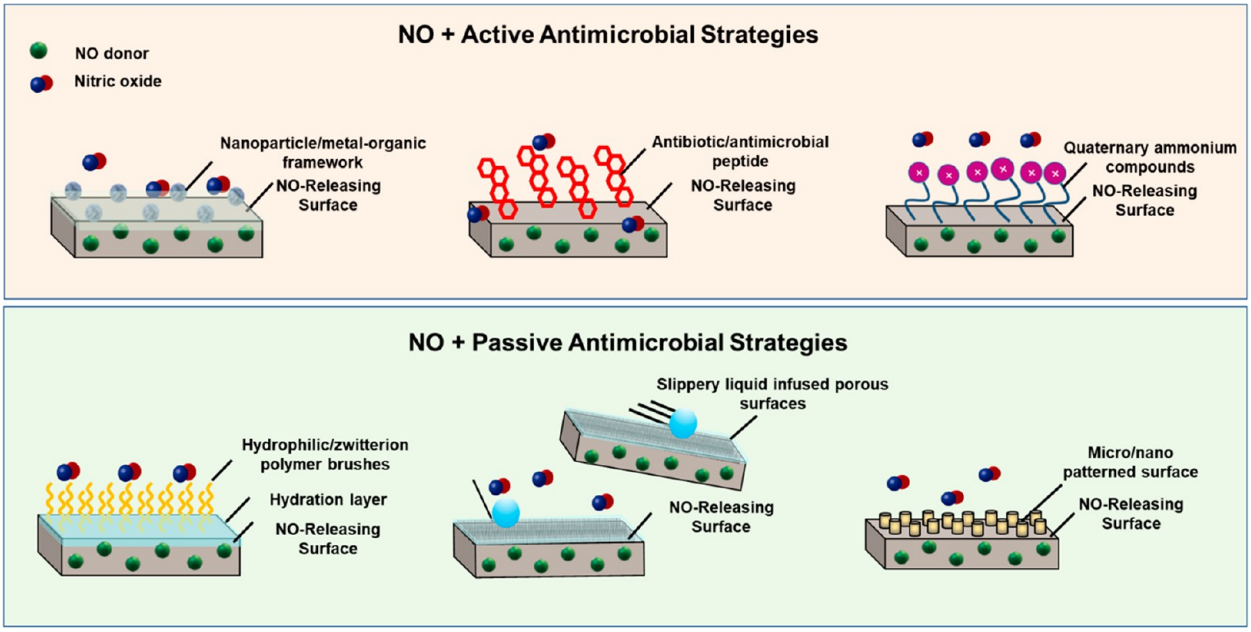

Figure 12. Different physical and chemical modification techniques to incorporate multifunctional antibacterial and antifouling surface properties into nitric oxide-releasing materials. These strategies include surfaces with nanoparticles, metal−organic frameworks, antibiotics, antimicrobial peptides, and quaternary ammonium compounds for antibacterial action. Antifouling surfaces include hydrophilic/zwitterionic polymer brushes, slippery liquid-infused porous surfaces, and surface patterning with micro- and nano-topographies.

Table 4. List of NO-Releasing Medical Devices/Polymeric Surfaces Exhibiting Dual-Action Antibacterial Behavior

strategy	secondary component	microorganisms	material/device	ref
antibacterial	formaldehyde	*S. aureus*, *E. coli*	micellar nanoparticles	216
antibacterial	dihydropyrrolones	*S. aureus*, *P. aeruginosa*	fluorinated ethylene propylene surface	217
antibacterial	β-defensin 2 (BD-2), colistin, gentamicin, chloramphenicol, ciprofloxacin, tetracycline	*P. aeruginosa*	catheter	188
antibacterial	tobramycin, meropenem, colistin, ciprofloxacin, ceftazidime, aztreonam,	*S. aureus*, *P. aeruginosa*, MRSA, *Burkholderia cepacia* complex, clinical-resistant *K. pneumoniae*, *P. aeruginosa*	chitosan oligosaccharides	186
antibacterial	CuNPs	*S. aureus*, *P. aeruginosa*	PU composites	168
antibacterial	CuNPs	*S. aureus*, *P. aeruginosa*	PVC tubing	175
antibacterial	Ag^+	*S. aureus*, *P. aeruginosa*	xerogel	177
antibacterial	AgNPs	*S. aureus*, *E. coli*, *S. mutans*	alginate NPs	218
antibacterial	benzophenone-based quaternary ammonium	*S. aureus*, *P. aeruginosa*	PU composites	194
antibacterial	selenium	*S. aureus*, *E. coli*	PU composites	174
antibacterial	chlorhexidine	*S. aureus*, *E. coli*	silicone rubber	170
antibacterial	nisin	*S. aureus*, *E. coli*	silicone rubber	169
antibacterial	heparin	*S. aureus*	silicone rubber	219
antibacterial	quaternary ammonium epoxides	*S. aureus*, *P. aeruginosa*	functionalized silica nanoparticles	220
antibacterial	quaternary ammonium	*S. aureus*, *P. aeruginosa*	poly(amidoamine) (PAMAM) dendrimers	192
antibacterial	oligo(ethylene glycol), hydrophobic ethylhexyl, cationic primary amine-containing antimicrobial polymer	*P. aeruginosa*	amphiphilic statistical ternary copolymer	130
antibacterial	amphotericin B	*S. aureus*, *E. coli*, *C. albicans*	PDMS	190
antifouling	ordered submicron pillar topographical surface	*S. aureus*, *P. aeruginosa*, *S. epidermidis*, *E. coli*	PU surface	213
antifouling	ordered submicron pillar topographical surface	*S. epidermidis*	PU surface	215
antifouling	silicone oil	*S. aureus*, *P. aeruginosa*	silicone rubber tubing	205
antifouling	silicone oil	*S. aureus*	silicon Foley catheter	207
antifouling	silicone oil	*S. aureus*, *S. epidermidis*	insulin cannula	25
antifouling	BPMPC	*S. aureus*	PU composites	210
antifouling	BPMPC	*S. aureus*	vascular catheters	211
antifouling	tecophilic SP60D60, hydrophilic, antifouling polymer	*S. aureus*	PU coatings	159
antifouling	hydrophobin SC3	*S. aureus*	PU−PDMS composites	189
antifouling	PDMS	*S. aureus*	PDMS surface	198

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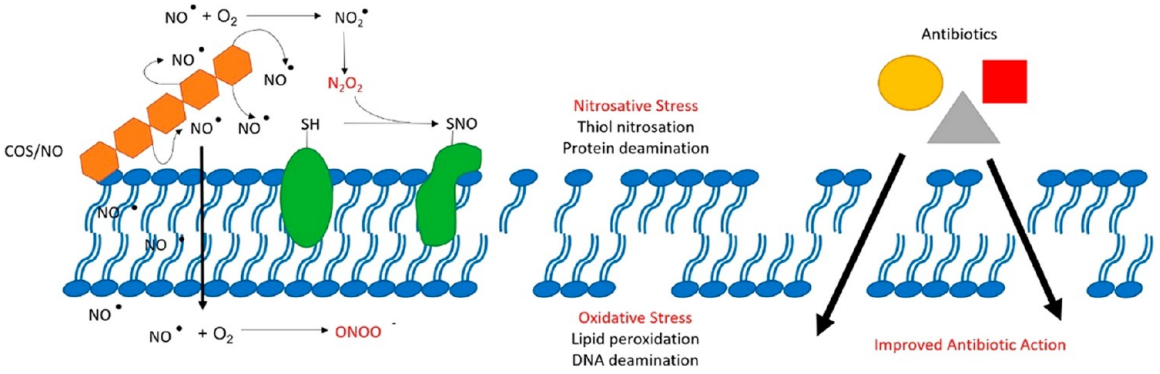

Figure 13. Antibiotic susceptibility in resistant bacterial strains can be enhanced by the action of oxidative and nitrosative stress generated by exogenous nitric oxide. Reproduced from ref 186. Copyright 2020 American Chemical Society.

antibacterial agents such as nanoparticles,[168] antibiotics, antimicrobial peptides,[169] and other antiseptic molecules.[170] The reported studies usually contain a NO donor incorporated into the base polymer, which is top-coated with a polymer containing secondary active molecules (see Table 4).

4.1.1. NO-Releasing Surfaces with Metal Nanoparticles. The advantage of having antibacterial nanoparticles as a secondary active mechanism serves a dual purpose with NO-releasing materials. Metal nanoparticles are known to catalyze the release of NO from *S*-nitrosothiol-based NO donor compounds because of their ability to break the S−NO bond of the donor. Metals like copper have been demonstrated to facilitate RSNO decomposition *via* Cu^{+} interactions, thereby leading to NO release from the donor.[154,171] In one example, NO-releasing biocompatible polyurethane composites were generated by incorporating 10 wt % SNAP into CarboSil-20 80A, a commercially available biomedical-grade polymer followed by a top coating of 1, 3, or 5 wt % CuNPs. Here, the SNAP molecule worked as a NO-releasing (NOrel) material, whereas the CuNPs worked as a NO-generating (NOgen) material.[168] The top coat of CuNPs not only helped to enhance the NO release but also improved the overall antimicrobial activity *via* the oligodynamic effect of Cu.[172] The NO flux for the SNAP−CarboSil composites without CuNP coatings after 3 h was found to be $(1.32 \pm 0.6) \times 10^{-10}$ mol min^{-1} cm^{-2}, whereas, with 1, 3, and 5 wt % CuNP coatings, it was observed to be $(4.48 \pm 0.5) \times 10^{-10}$, $(4.84 \pm 0.3) \times 10^{-10}$, and $(11.7 \pm 3.6) \times 10^{-10}$ mol min^{-1} cm^{-2}, respectively. Although the CuNPs-only controls exhibited some antimicrobial effects, the 3% Cu−SNAP composites exhibited a significant reduction (up to 99.8%) in both Gram-positive *S. aureus* and Gram-negative *P. aeruginosa* relative to the controls. Various other studies have shown the use of nanoparticles as a catalyst and a means to generate NO, using zinc, copper, and selenium to enhance the antibacterial efficacy with a variety of NO donors.[173−175] The combination of CuNPs and NO has been shown to increase antimicrobial effects and blood compatibility for short-term extracorporeal circulation (ECC) applications.[175] Combinational approaches involving metal nanoparticles can be extremely advantageous for the catalytic release of NO from medical-grade polymers. The innate bactericidal efficacy and ability to interact with endogenous RSNOs in blood makes CuNPs superior to other types of metallic nanoparticles. Similarly, the broad-spectrum antimicrobial properties of NO have been combined with ZnNPs to sterilize the hub regions of tunnel dialysis catheters.[176] The Meyerhoff group developed a novel NO-releasing insert for hemodialysis catheter hub disinfection in which ZnNPs combined with GSNO significantly increased the NO flux, and this device demonstrated superior antimicrobial activity in a full-length catheter implanted in a 14 day *in vivo* sheep model compared with clinically used chlorhexidine-impregnated caps. Other literature has reported the potential for synergistic killing by NO with Ag, which has also been explored against infection-causing pathogens for biomedical applications.[177]

While metal nanoparticles can trigger higher levels of NO surface flux, they also have the potential to generate a consequent cytotoxic effect from the leaching of these particles.[178] This undesired leaching can harm the neighboring cells and healthy tissues, leading to inflammatory reactions in the body. To overcome the challenge of metal leaching, copper-based metal−organic frameworks (MOFs) have been reported to alleviate $Cu^{2+/1+}$ *via* coordination with extended catalytic operation as opposed to their salt or nanoparticle counterparts. The use of MOFs in NO-releasing polymeric composites with NO donor compounds was demonstrated by the creation of a multifunctional triple-layer composite scaffold with CuBTTri and SNAP.[179] The NO release levels from the catalyzed SNAP decay could be finely tuned by varying the concentration of CuBTTri. These combinational NO-MOF surfaces demonstrated 2.74 and 1.23 log reduction in adhered MRSA and *E. coli*, respectively.[179] Although these surfaces showed improved antibacterial properties compared with the individual NO or MOF control surfaces, the practical use of MOF-containing materials has been restricted because of high production rates, inadequate selectivity, minimal function, and complexities in recycling/regeneration.[180] Similar studies involving a combination of NO and a nanocomposite poly(vinylidene fluoride) (PVDF) membrane or other light-activated antibacterial nanomolecules have been reported.[181−184] These metal-based surfaces can be irradiated with a light source, taking advantage of the photocatalytic activity to increase the therapeutic efficacy of NO-releasing surfaces. Readers are directed to other thorough reviews for more information on NO-releasing photoactivable materials for antibiofilm applications.[185]

4.1.2. NO-Releasing Surfaces with Antibiotics, Antiseptics, or Antimicrobial Peptides. Many studies in the past have reported the efficiency of NO-releasing materials in eradicating viable bacteria and their ability to maintain a biofilm-free state for an extended period of time.[37,157] It has been demonstrated that NO can increase the susceptibility of multiple classes of antibiotics in drug-resistant bacteria while simultaneously slowing down the resistance process.[186] This can be attributed to the augmented membrane permeability in

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bacteria caused by reactive oxygen and nitrogen species generated by exogenous delivery of NO. It is hypothesized that an increase in membrane permeability driven by NO can result in better action of antibiotics in bacteria (Figure 13). For this reason, scientists have attempted to either modify the NO-releasing surface with broad-spectrum antibiotics[187] or improve the antibacterial properties of NO by codelivery/subsequent delivery of antibiotics after NO treatment.[187,188] The Schoenfisch group has studied the combined effects of NO with various antibiotics in chitosan oligosaccharides.[186] Their study confirmed that most combinations of NO and antibiotics were synergistic or additive, without any antagonism, demonstrating the synergy of the approaches and advantages of their combination.[186] These strategies can prove to be superior against antibiotic-resistant pathogens such as *P. aeruginosa*, which have lower permeability to conventional antibiotics, the presence of efflux pumps, and production of enzymes that can chemically alter the expression and deactivate the action of antibiotics.

Despite the excellent broad-spectrum antimicrobial, antithrombotic, and anti-inflammatory properties of NO, the commercialization of NO-releasing materials has not been achieved to date. Hence, approaches that involve other clinically available antimicrobial catheter materials have also been combined with NO-releasing properties to create multifunctional medical device interfaces for a greater level of microbial eradication. Recently, a method to modify silicone rubber medical device interfaces to incorporate the NO donor SNAP and the commonly used broad-spectrum antiseptic chlorhexidine (CHXD) was reported.[170] The antiseptic CHXD was top-coated on the SNAP-loaded surface at various concentrations. The CHXD was homogeneously dispersed on the surface of the films, and its mechanism of action is that it can kill pathogens upon contact, thereby preventing biofilm formation on the surface. The dual-active SNAP−CHXD surfaces demonstrated the highest reduction in viable *S. aureus* and *E. coli* bacteria with >3 log reduction on the surface of the films with up to 4 weeks of physiologically relevant levels of NO.[170] A similar methodology has been used by other groups to immobilize hydrophobin and amphotericin-B on NO-releasing surfaces for bacterial and fungal eradication.[189,190] The fate of the medical device is highly dependent on the initial time point of implantation or insertion, where prevention of microbial adhesion on the surface is determined to be very crucial. The synergy of multiple antimicrobial interfaces can radically reduce the attachment of viable bacterial cells on the surfaces. The successive levels of NO release from the surface can then persistently offer antibacterial action against clinical pathogens and help maintain a biofilm-free state.

4.1.3. NO-Releasing Surfaces with Quaternary Ammonium Compounds. Ionic compounds such as quaternary ammonium, phosphonium, phosphonic acid, and sulfonic acid organic compounds are well-known for their antimicrobial activities. When these charged molecules are combined with NO donors, the antimicrobial effect of the materials increases significantly.[191] Since long alkyl chains on QACs have been shown to increase the penetration of molecules into the bacterial cell membrane, NO-releasing QAC-functionalized generation 1 (G1) and generation 4 (G4) poly(amidoamine) (PAMAM) dendrimers using the NONOate form of NO donors have also been reported.[192] Modification of QAC dendrimer scaffolds with NO release capabilities resulted in increased bactericidal efficacy against both Gram-positive and Gram-negative bacteria compared with the QAC-modified dendrimers alone.[192,193] The NO payload in these materials can be tuned by regulating the polarity of the charging solvent used in the NONOate synthesis reaction (*i.e.*, by increasing the ratio of tetrahydrofuran to methanol with increasing alkyl chain length). However, the stability of polymers with NONOates during shelf storage and with various hospital sterilization methods is yet to be evaluated. To overcome this, a combination of RSNO and QAC was synthesized that demonstrated a superior bactericidal effect by permanent photo-cross-linking and surface immobilization of benzophenone-based quaternary ammonium antimicrobial (BPAM) on a CarboSil-based polymeric composite with SNAP embedded as a NO donor.[194] SNAP has the capacity to crystallize in the polymer matrix and be triggered *via* heat, light, or metal ions. The crystallinity of the donor in the polymer matrix increases its lifetime in the RSNO-loaded polymers up to 8 months of storage at room temperature.[195] Because of its excellent storage capacity, the dual-functional polyurethane polymer CarboSil 20 80A was loaded with the NO donor SNAP followed by top coating with surface-immobilized BPAM molecule. BPAM exhibits instant contact killing and high biocidal activity against both Gram-positive and Gram-negative bacteria along with rapid surface attachment (within 1 min) to the polymer with mild UV irradiation and good mechanical durability.[194]

4.2. NO-Releasing Combinational Surfaces with Antimicrobial and Antifouling Strategies

A second potential limitation of NO-releasing polymers, and motivation for their combination with antifouling strategies, is they have been shown to promote surface fouling *via* blood protein adsorption.[196] As previously mentioned, such non-specifically adsorbed physiological proteins often become a substrate for bacteria attachment, which adversely influences the performance of NO-releasing materials. Although the adsorption of protein on the surface does not affect the activity of NO release from polymers,[174] it can increase surface fouling arising from dead bacterial debris. Therefore, a secondary antifouling mechanism that eliminates the fouling on the NO-releasing device surface that encounters bodily fluids while actively killing bacteria *via* NO is one of the newest and most promising directions in this field of research. The antifouling approaches applied to NO-releasing materials include texturing of the polymer surface, liquid-infused slippery surfaces, conjugation of NO donors on polymeric brushes, and NO-impregnated/incorporated surfaces with zwitterionic, superhydrophobic, and even hydrophilic top coats.[25,197]

4.2.1. NO-Releasing Hydrophilic and Hydrophobic Antifouling Surface. Because of their intrinsic antifouling property, hydrophilic coating materials play a crucial role in combating microbial growth on the surface. When a hydrophilic surface comes in contact with bodily fluid, a hydration layer is formed on the surface that inhibits the attachment of nonspecific hydrophobic proteins. Furthermore, the combination of NO-donating materials and antifouling surfaces exhibits a synergistic antimicrobial effect. This method was demonstrated by a polyurethane coating with antibacterial and antifouling properties using CarboSil 2080A polymer and SNAP as the NO donor.[159] The developed CarboSil−SNAP composite was top-coated with Tecophillic SP60D60, a commercially available hydrophilic antifouling polymer with a contact angle of *ca.* 51°. The fabricated coating showed sustained NO release and a synergistic effect in the reduction of up to 96% of the *S. aureus*

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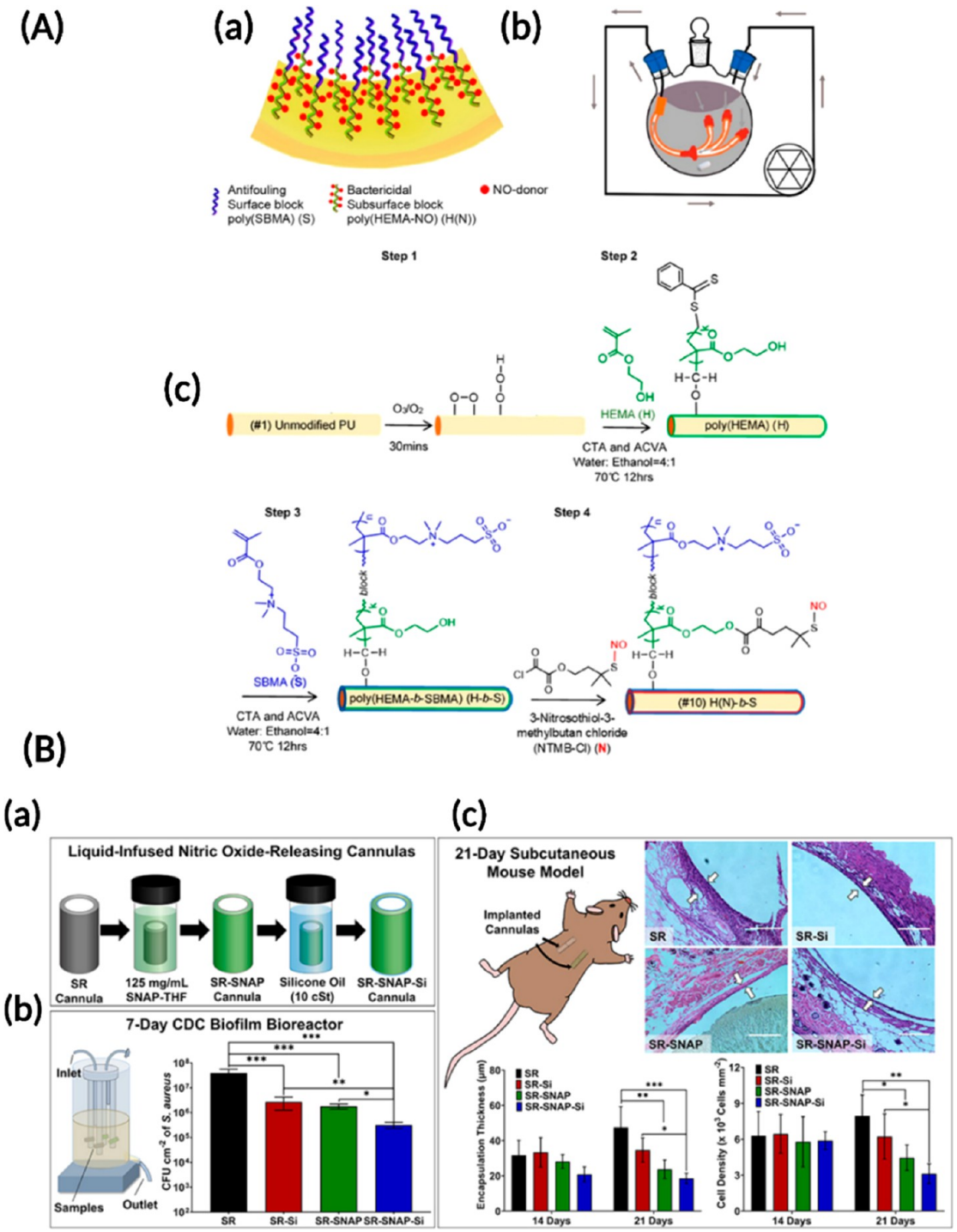

Figure 14. (A) Synthesis and reaction scheme for a NO-releasing diblock copolymer brush (H(N)-*b*-S) grafted on a polyurethane (PU) catheter. (a) The diblock copolymer brushes with NO-releasing properties are modified using poly(HEMA) (H) with *S*-nitrosothiol (N) and the antifouling compound poly(SBMA) (S). (b) Design and representation of the flow reactor for modifying the surface of a clinically relevant-sized catheter (the gray arrow represents the direction and flow of the monomer solution). (c) Synthesis route to generate a NO-releasing diblock copolymer coat using ozone pretreatment followed by surface-initiated RAFT diblock copolymerization. Reproduced from ref 200. Copyright 2020 American Chemical Society. (B) (a) Schematic representation of the development of liquid-infused NO-releasing cannulas. (b) The cannulas were tested in a CDC bioreactor for up to 7 days and were found to prevent *S. aureus* bacterial adhesion by 99.2% reduction on the surface of the cannula. (c) SR-SNAP-Si cannulas radically decreased the thickness of the fibrous encapsulation surrounding the implant in the mouse model after 21 days by 60.9 ± 6.1% relative to unmodified cannulas. Reproduced from ref 201. Copyright 2021 American Chemical Society.

viable cell count compared with the control samples. A biomimetic surface coating on NO-releasing polymers was also evaluated for antimicrobial applications. This methodology included solvent impregnation of SNAP in CarboSil and PDMS polymer followed by a top coat of hydrophobin SC3 (SC3), a self-assembling amphiphilic protein.[189] The top-coated SC3 led to β-sheet formation on the CarboSil surface that induced hydrophilicity, resulting in a *ca.* 30% reduction in the contact

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angle (from 107° to 76° for SC3−SNAP−CarboSil). The change in surface wetting also resulted in a 10-fold drop in the fibrinogen adsorption on SC3-top-coated polymer samples compared with non-SC3-coated samples. The SC3-top-coated SNAP−PDMS polymer samples demonstrated a superior bactericidal property, with a *ca.* 79% reduction in viable *S. aureus*. However, one of the major constraints with using polymers for top-coating of the substrates is the potential for untimely polymer degradation, as it can lead to an increase in surface roughness or a non-homogenous top-coat layer, which can defeat the purpose of having an antifouling interface.

Surface immobilization of NO donors has greatly impacted the field, and a major advantage of combining antibacterial and antifouling strategies is accomplishing the long-term function of medical devices. The presence of an antifouling interface has been understood to prolong the life of NO-releasing materials even after the total NO payload is exhausted in the polymer matrix. This was exemplified with a triple-action (protein-, platelet-, and bacteria-repellent) coating called surface-immobilized *S*-nitroso-*N*-acetylpenicillamine (SIM-S) on a PDMS polymer surface to combat infection.[198] The modified PDMS polymers released NO at physiologically relevant levels for up to 4 weeks, resulting in a 99.99% (∼4 log) reduction in viable *S. aureus* over 24 h. The functionalized polymer surfaces revealed the non-fouling nature and significantly reduced protein adhesion by *ca.* 65% compared with unmodified PDMS. The antifouling capability of the material surface was preserved despite the complete depletion of the NO payload within the polymer because of the surface-immobilized *N*-acetylpenicillamine degradation product.

Similarly, the use of mussel adhesive chemistry *via* polydopamine (PDA) immobilization of polytetrafluoroethylene (PTFE) particles on the SNAP-loaded NO-releasing polymer composite surface was recently reported.[199] The PTFE coating on the NO-releasing surface decreases the surface wettability of the polymer, making it highly hydrophobic. On very hydrophobic surfaces like the PTFE coating, air−water interfaces or the presence of interfacial nanobubbles can significantly reduce the contact of bacteria with the surface. Therefore, the PTFE coating is known to passively lower the degree of bacterial attachment to the surface of the polymer, and the presence of active NO release is expected to eradicate bacteria that are able to adhere to the surface. The combination of these two interfaces was shown to reduce 99.3% and 99.1% of viable *S. aureus* and *E. coli* bacteria on the surface, respectively.

Despite the integration of multiple mechanisms in a single medical device, NO-releasing materials suffer from limitations such as a lower range of NO release levels, leaching of the NO donor from the polymer, and clinical/commercial translatability. Many approaches reported in the literature need to be scalable, easy to manufacture, and ready for the regulatory pathway for effective clinical translation. From a broader perspective, blood-contacting devices frequently face the problem of clotting, which is often linked with device-associated infection. One major advantage of NO-releasing devices is their diverse role in various biological pathways. Combinational surfaces with NO-releasing properties are superior to other surfaces because of the multiple roles of NO (vasodilation, platelet activation, inflammation, pathogen elimination, *etc.*). To demonstrate this, Hou *et al.* reported a NO-releasing catheter with uniform high-density precision diblock copolymer brushes (termed H(N)-*b*-S) consisting of a surface block of antifouling poly(sulfobetaine methacrylate) with a subsurface block of antibacterial RSNO-modified poly(hydroxyethyl methacrylate).[200] By the use of a novel catheter modification technique of ozone-initiated surface reversible addition−fragmentation chain-transfer (ozone-surface-RAFT) block copolymerization, both the inner and outer surfaces of a slender PU catheter were altered. These dual-functional NO-releasing catheters exhibited 99.99% biofilm reduction of various Gram-positive and Gram-negative bacteria, compared with <90% antibacterial activity of a commercial silver catheter in a murine subcutaneous infection model. In a long-term study, these modified catheters exhibited >99.99% reduction in MRSA bacteria in a 5 day implantation study in a porcine central venous catheter infection model. In addition, the combination of NO and polymer brushes demonstrated excellent antithrombogenicity and biocompatibility. More importantly, this study presented a technique to design a flow reactor to scale up the H(N)-*b*-S coating procedure to modify a catheter with a clinically relevant size (30 cm long) (Figure 14A). Overcoming these challenges in scaling up the synthesis of material design along with the combination of the secondary antimicrobial approach is expected to significantly enhance the translatability of NO-releasing materials for clinical applications.

4.2.2. Liquid-Infused NO-Releasing (LINORel) Surface.

Although impregnation with the NO donor does solve the issue of treating the bacterial infection, it does not completely resolve the issue of fouling from proteins of dead bacteria. When it comes to designing biocompatible coatings, materials scientists are often drawn toward biomimetics to explore and construct materials inspired by natural phenomena. Strategies to mitigate bacterial colonization on device surfaces are urgently needed that are equipped with synergistic elements like surface chemistry and surface roughness that are unfavorable for bacterial attachment. With this in mind, there has been tremendous growth in the development of slippery liquid-infused porous surfaces (SLIPs).[202,203] These surfaces are a new class of antifouling materials inspired by the gastrointestinal tract that take advantage of van der Waals and capillary forces between the fouling liquid and infused polymer. Together these forces generate an atmosphere in which they actively favor the infusing liquid as opposed to the fouling fluid, resulting in a continuous infused surface. The SLIP materials provide an antifouling approach to resist the adhesion of pathogenic microorganisms and proteins without affecting the NO release, which can be achieved by infusing the polymer with biocompatible silicone oil (Si oil).[204]

NO-releasing medical devices made of silicone rubber polymer have shown promising ability to be infused with Si oil to create an antimicrobial and antifouling interface.[25,201,205,206] Such surfaces can be impregnated with the NO donor SNAP and then later infused with Si oil to generate the antifouling surfaces (Figure 14B). Reports suggest that infusion with Si oil not only improved the controlled release of NO but also reduced the leaching of SNAP while maintaining the ultralow fouling property of the liquid-infused silicone tubing surface.[205] Furthermore, the liquid-infused NO-releasing (LINORel) surface exhibited 99% and 88% reduction in viable cell adhesion of *S. aureus* and *P. aeruginosa*, respectively, over 7 days in a CDC bioreactor environment.[205] Moreover, the fabricated NO-releasing non-fouling surface was also found to be non-cytotoxic toward mammalian fibroblast cells. A similar methodology was reported with other SR-based medical devices for the use of urinary catheters and insulin cannula with long-term NO release and reduced SNAP leaching and protein fouling in addition to excellent antibacterial, antifouling, and biocompatible proper-

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ties.[25,201,207] This is a simple and promising approach to generate a LINORel surfaces on prefabricated medical devices and therefore holds huge potential in clinical translation. Recently, a novel method to generate NO-releasing Si oil with proactive antibacterial properties was reported that involved covalent immobilization of the NO donor to Si oil or generation of NO-releasing Si oil by nitrosation of thiolated Si oils.[208,209] Such oils can be infused on the PDMS surfaces that are often used for biomedical device applications to create antibacterial interfaces. NO release from these surfaces can be controlled by modulating the NO payload on the basis of the type of application. These studies confirmed the ability to tune the NO surface flux by altering the percent thiol conversion to NO moieties in the NO-releasing Si oil.[208]

4.2.3. NO-Releasing Surface with Zwitterionic Properties. To augment the efficacy of NO-releasing surfaces, antifouling zwitterionic-based compounds have been employed. To explore the covalent grafting of zwitterionic polymers onto various substrates ranging from hydrophilic to hydrophobic, benzophenone (BP) chromophore, a photoactive tethering reagent, was incorporated into the polymer backbone.[210] The covalent grafting of the synthesized antifouling zwitterionic terpolymer, 2-methacryloyloxyethyl phosphorylcholine-*co*-butyl methacrylate-*co*-benzophenone (BPMPC), to SNAP-incorporated CarboSil through rapid UV cross-linking resulted in a stable hydrophilic coating (contact angle ∼ 50°) with antimicrobial ability and excellent antifouling properties. The developed zwitterionic coating material showed a significant reduction in protein adhesion (*ca.* 84−93%) compared with the control samples. A similar trend was observed for a SNAP-incorporated CarboSil composite with BPMPC top coat, which also exhibited a 99% reduction of viable *S. aureus* compared with the control samples. Facile treatment of a phosphorylcholine-based polyzwitterion and its covalent attachment to a hydrophobic CarboSil polymer also inspired the fabrication of antimicrobial, anti-inflammatory, and antithrombotic vascular catheters.[211] The SNAP−BPMPC catheters released NO above physiological levels for over 1 week, exhibited a significant reduction in viable *S. aureus* (97%) after 7 days in a CDC bioreactor environment, and also demonstrated excellent hemocompatibility in an *in vivo* rabbit model over a 7 day period.

4.2.4. NO-Releasing Surface with Topographical Patterns. Nano- or microtopographies in combination with NO release have been demonstrated to be useful methodologies to prevent and manage bacterial attachment and biofilm development on a polymeric substrate. While the patterns can inhibit bacterial attachment in the initial time points, NO with biocidal properties can actively kill the bacteria and disperse the biofilms over longer durations.[212,213] These strategies can inhibit medical-device-related infections with no known antibiotic resistance. When the NO-releasing materials are incorporated into the physically modified surfaces, they exhibit an enhanced dual-function antimicrobial property with reduced foreign body response.[212−214] This phenomenon was verified with a textured polyurethane-based film containing SNAP as the NO-releasing material in the sublayer and an ordered sub-micrometer pillar topography at the top surface.[215] A series of SNAP-textured films with CarboSil 20 80A polyurethane were developed, in which the middle layer of PU was doped with 5, 10, or 15 wt % SNAP and the top surface layer was textured with patterns of 400/400 nm or 500/500 nm using a soft lithography two-stage replication molding technique. The hydrophobicity of PU was seen to increase as a result of surface texturing (the water contact angle changed from 91° to 139°). The NO release rate, reduction in bacterial adhesion, and biofilm formation were in correlation and directly proportional to the SNAP concentration in the sublayer. A synergistic effect on the inhibition of *S. epidermidis* bacterial adhesion due to the combination of NO release and surface texturing was observed. The biomimetic SNAP textured CarboSil PU surface containing 15 wt % SNAP and the 500/500 nm pattern surface texture reduced the bacterial adhesion by 88% and inhibited biofilm formation for at least 28 days. However, one disadvantage of the repeated spin-coating process was that depositing the SNAP−polymer solution onto a dried SNAP−polymer surface can cause redissolution and recrystallization of the NO donor, instigating untimely degradation during the fabrication method. To reduce the loss of activity, a new method that utilized impregnation of SNAP on a textured polymer surface was recently reported.[213] The 700/700/300 nm surface texture alone reduced the surface-bound bacteria counts by 49%, 28%, 52%, and 27% for *P. aeruginosa*, *S. aureus*, *S. epidermidis*, and *E. coli*, respectively, after only 1 h of incubation. However, the 15 wt % SNAP-impregnated samples in the 700/700/300 nm textured surface reduced the degree of bacterial adhesion with inhibition rates of 88%, 61%, 85%, and 85% for the same four bacteria strains over the 1 h test period, corroborating the synergistic effect of SNAP and the textured surface toward the reduction of bacterial adhesion to the polymer surface.

5. CONCLUSIONS AND FUTURE OUTLOOK

The recent progress in biomaterials science and biomedical engineering has led to the development of robust dual-function antibacterial surfaces. These materials contain dual antimicrobial strategies combined into one system with either two active antimicrobial actions (active−active) or an antimicrobial action combined with an antifouling action (active−passive). The literature research done in this review confirms that the recent developments made in producing dual-functional surfaces can synergistically enhance the antibacterial effect of other antibacterial agents such as antibiotics, metal nanoparticles, or nitric oxide, showing more effective antibacterial therapy compared with traditional monofunctional surfaces. While active−active approaches might be better suited for shorter-term device applications since their antimicrobial reservoir will become depleted over time, the active−passive approaches have the advantage of initial active antimicrobials to fight initial infection while the passive moieties can continue protecting the surface longer (provided that the antifouling chemistry is stable). This can be a crucial issue in medical devices with long-term implantation, such as heart valves, that can get seriously infected years after the surgery, which might necessitate a long-term solution. Ultimately, the specific material requirements have to be considered for the final medical device application since not all dual-functional materials may be the best approach to address infection challenges universally for all medical device applications. For example, the antiadhesive/antifouling materials approaches may have limitations in orthopedic applications because it is a significant challenge to fabricate an implant that inhibits bacterial colonization and concomitantly promotes osteoblast adhesion. However, combinational surfaces with such mechanisms might prove beneficial for urinary and intravascular catheters that do not require such prerequisites. In fact, vascular catheters require inhibition of the attachment of platelets and plasma proteins (albumin, fibrinogen, fibronectin, *etc.*) on the device surface. It is understood that the adsorption of proteins

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can trigger platelet activation and blood clotting, which is highly undesirable for blood-contacting devices. Similarly, the microenvironment of the urinary catheter implant site may contain proteins and electrolytes that may accumulate over time and negatively impact the function of the urinary catheter. Therefore, having a combinational surface with both antimicrobial and antifouling strategies can significantly prevent the adhesion of biomolecules in addition to actively eradicating bacteria, all of which can improve the function and lifetime of the device.

Strategies involving metal nanoparticles, antibiotics, or QACs integrated with antifouling mechanisms like polymer brushes and topographies have been seen to exhibit promising activity in the initial microbe exposure time points. However, the success rate of these medical devices *in vivo* for long-term applications has been limited because of other underlying biological issues associated with medical devices (*e.g.*, thrombosis and inflammation). Since medical-device-related infection is a complex series of steps, many of these materials still lack the universal properties needed to prevent biofilm formation on the device surface. Moreover, most contact-killing biocides have a higher probability of failing against superbugs with multidrug resistance. To overcome these problems, nitric oxide (NO)-releasing polymers have been extensively explored in the field of biomedical engineering for their therapeutic efficiency. These materials have not only exhibited synergistic effects when combined with other antimicrobial/antifouling strategies against clinically resistant bacterial strains but also demonstrated the ability to address multiple biocompatibility challenges, including thrombosis and inflammation, without any reported cytotoxicity or resistance concerns. Furthermore, NO-releasing materials alone have been promising in both short- and long-term animal models;[160,221] however, a potential limitation with other dual-functional materials reported in the literature is that similar animal studies have not yet been conducted.

Even with significant growth in the development of antimicrobial surfaces with multiple functionalities in the literature, to date not many platforms have accomplished clinical translational success. This can possibly be related to the functions and properties of multifunctional biomedical devices in long-term applications and severe gaps in meeting the requirements of translational research. There is also no comprehensive evidence in the studies reviewed detailing how the dual-functional materials would affect the resistance mechanisms in the biofilm-forming pathogens. Therefore, future studies with dual functionality should consider studying the long-term cytotoxic effects, biocompatibility, and bacterial resistance of the developed material, primarily for *in vivo* applications in clinically applicable models (*e.g.*, specific medical device applications).

All of the bactericidal agents have their respective disadvantages relating to their shelf-life stability, limited advancement to *in vivo* application, long-term effectiveness, biocompatibility, cost, and ease of synthesis. Moreover, as seen with the topographical designs, not all structures are effective against all types of bacteria, and more importantly, these surfaces have not been tested in long-term animal models. Many of these approaches need to be scalable to medical devices of clinically relevant size, easy to manufacture, and well-prepared for the regulatory pathway in order to be translated to clinical use in patients. Although some materials reported in the literature might seem promising with small-scale *in vitro* studies, the translatability of some material designs remains a challenge. Since biological microenvironments are known to be considerably complex, it is imperative to evaluate the dual-functional biomedical materials and devices discussed here for their antimicrobial performance in end-use medical device applications.

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