Nanoscience-Led Antimicrobial Surface Engineering to Prevent Infections

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Abstract

One of the major complications associated with the implantation of biomedical devices regardless of their function is biomaterial associated infection. Infections are generally initiated by opportunistic bacterial colonization and biofilm development on the surface of implanted biomaterials, rendering the infection impervious to host defenses and antimicrobials. Moreover, the infection around soft tissues also has a significant role in biomaterial-associated infections. It is well documented that the nature of an implant infection is influenced by the design and composition of the implant biomaterial, host environment, clinical procedure and patient hygiene. Herein, we explore the adhesion mechanisms of bacteria to the biomaterials and review systematic antimicrobial strategies to reduce the contamination of biomaterials and underlying implant infection using *Staphylococcus aureus* as a model bacterial pathogen. Also, we discuss the preventive and therapeutic strategies and explain the future perspectives for the development of nanoscience-based strategies for the engineering of antimicrobial surfaces, including nanostructure surface, microbe-surface interactions, synthetic nanostructured surfaces, dynamic surfaces with antifouling agents, coated surfaces with antimicrobial properties (polymer coating, surface release active coating).

Keywords: Nanoscience, Antimicrobial strategies, biomaterials, infection propensity, medical device infection, mechanism of adhesion

1. Introduction

Biomaterials are defined as "materials designed to take a form that can direct, through interactions with living systems, the course of any therapeutic or diagnostic procedure" [1]. Biomaterials are designed to replace hard or soft tissue that is damaged and malfunctioned through different circumstances such as fracture, infection, cancer cells, organ failure, or other pathological processes [2,3]. Biomaterials must be biocompatible and capable of functioning like normal tissue both physically and biochemically. Furthermore, they should be neither carcinogenic nor toxicogenic and have efficient physical and mechanical properties to serve as a long-term replacement of the respective body tissue. Medical devices are described by the Food and Drug Administration as "a machine, apparatus, instrument, implement, *in vitro* reagent, contrivance, or other similar or related object, including an accessory or component part which is recognized in the United States Pharmacopeia, or office National Formulary, or any supplement to them" [4,5].

Modern medical devices play an important role in healthcare for both detection and treatment purposes; however, the use of such devices including implants and catheters can result in increased risks of infections. There is a high rate of colonization of abiotic surfaces of biomaterials because of the induction of microorganisms which form biofilms that are highly resistant to antimicrobial treatment such as antibiotics [6,7]. Without biomaterials, tissue infection by opportunistic pathogens is usually suppressed by the immune system, but tissue infections caused by biomaterials activate a local tissue response, which consists of both chronic and acute inflammation because of the complexity of interactions between the host immune cells, microbial pathogens and the biomaterial that can cause the formation of granulation tissue and subsequent tissue fibrosis [8–12].

The microbial body flora mainly resides in the oral cavity, saliva, mucosa, ear canal, and gastrointestinal tract where they have a number of roles, including stimulating innate immune defense mechanisms against pathogenic bacteria. However, the growth and proliferation of these symbiotic bacteria can become uncontrolled and lead to localized and/or systemic infection in some situations. Whilst the human body can be infected by different pathogenic microorganisms (eg. viruses, protozoa and fungi), the most common type of acute and chronic infections are caused by bacteria [7,13], which is the focus of this review.

Bacteria can exist in planktonic and sessile states which display very distinct phenotypic and genotypic features. The adhesion of bacteria to a biomedical device surface is characterized by slime production coupled with rapid expression of genes responsible for exopolysaccharide production. This alteration initiates almost instantly following bacterial attachment and colonization of both abiotic and biotic surfaces, and causes biofilm formation that protects the bacteria from external substances (such as antibiotics and antimicrobial compounds) or the immune system [14,15].

This review discusses nanoscience-led antimicrobial strategies to inhibit biomaterial-associated infections (BAIs) and tissue infections. The mechanisms underpinning bacterial adhesion to biomaterials, biofilm development and the role of novel biomaterials in preventing implant-associated infections are also considered. Finally, future perspectives on antimicrobial medical device technology are highlighted with specific focus on deploying novel nanoscience-led strategies to reduce infections.

2. Adhesion of bacteria to biomaterials

Opportunistic pathogenic bacterial cells adhere to biomaterials through bacterial appendages such as pili or flagella [16]. A thin layer of conditioning film is essential to mediate this initial adhesion process on an indwelling medical device or infected tissue implant and this is often composed of polysaccharides, von Willebrand factor, collagen, laminin, vitronectin, thrombospondin, fibrinogen, and fibronectin (Figure 1). The two stages of bacterial adhesion are 1) primary unspecific and reversible adhesion and 2) specific irreversible adhesion. In the initial stage of adhesion, the weak interaction between bacteria and the surface causes a reversible process. The extent of bacterial adherence to the implant or tissue is dependent on the surface properties of the bacterial cell and the composition of the biomaterial. Adhesion is defined as the attachment of bacteria to the surface, while attachment between the cells is termed as cohesion [7,17].

Biomaterials can act as substrates for bacterial attachment and subsequent biofilm formation. This process is mainly due to steric interactions, hydrophobic interactions, electrostatic interactions, protein adhesion, and Van der Waal forces [7]. Adhesion to living tissues is a specific adhesion-based or lectin-based interaction, while adhesion to the abiotic surfaces is unspecific. Uncoated native surfaces are quickly coated by conditioning films which include immune protein components and extracellular matrix (ECM) when submerged in body fluids. Biomedical surfaces are also coated with protein from interstitial fluids and blood within nanoseconds, and this process is determined by the wettability of the biomedical device surface and surface chemistry. Overall, the predominant mechanism for bacterial attachment to biomedical devices within the body is adhesion [18–22] and it is this biological process which results in biomaterial-mediated bacterial infections and associated bacterial pathogenesis [23].

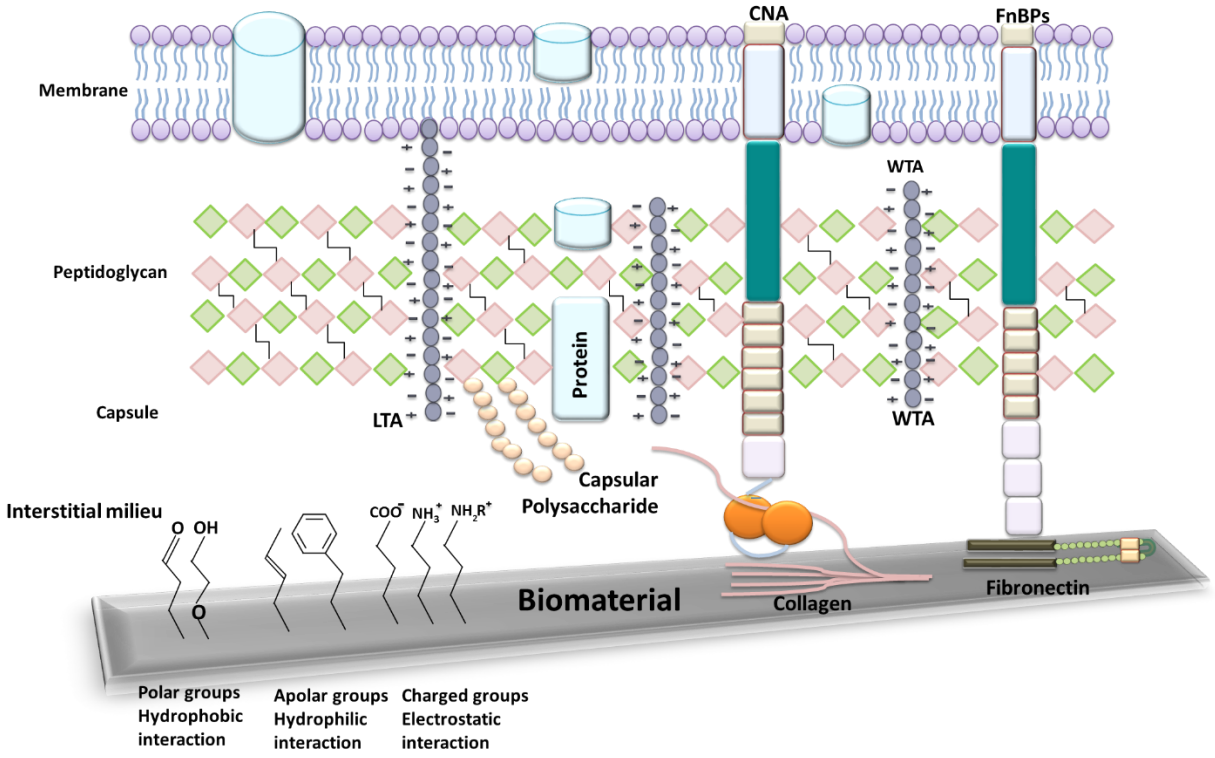

Figure 1 The attachment of bacteria to the surface of biomedical devices inside the body. The combination of irreversible active mechanism and reversible passive mechanism causes bacterial adhesion on the biomaterial surface. *Staphylococcus epidermidis* and *Staphylococcus aureus* possess many mechanisms for adhesion and biofilm development that result in virulence during chronic biomedical infection.

Adhesion to biomedical device surfaces

Primary bacterial adhesion to the biomaterial surface is mediated by nonspecific forces (electrostatic, Lifshitz–van der Waals, and Lewis acid-base forces), with bacteria behaving like colloidal micro-particles [24,25] which enables *in vitro* simulation [26]. Bacterial filamentous cell appendages, including nanofibers, bacterial pilus-like, and pili adhesive structures act as adhesins

[27,28]. Some bacterial nanofibers mediate attachment of the bacteria to the biomaterial surfaces and help in the formation of the biofilm. Other bacterial filamentous cell appendages which are involved in implant infections specifically bind to the host cell surface molecules, fibronectin and collagen respectively (Figure 1) [26]. Autolysis AtlE from *S. epidermidis* is a species-specific protein that can bind to both abiotic surfaces, like naked polystyrene and biotic surfaces, like vitronectin. Other species-specific proteins such as the autolysin AtlA from *S. aureus* has dual functionality that undergoes proteolytic cleavage to obtain an amidase and a glycosaminidases which are catalytically active proteins. Amidase interacts with the matrix proteins vitronectin, fibronectin, and fibrinogen. Therefore, AtlA mainly mediates attachment of *S. aureus* to implants that are coated by proteins in the host matrix which assists with biofilm formation. The autolysin AtlaA from *Enterococcus faecalis* also has a role in biofilm development as demonstrated by an *atlA* gene deletion mutant strain which lacks the ability to form biofilms [17].

3. Biofilm formation

It is predicated that approximately 70% of human bacterial infections are related to biofilm formation [29]. Indeed, bacteria are the most important factor in mediating BAIs [7]. Bacteria attach to the surface and develop a biofilm, after that the bacteria tightly and irreversibly attach to the surface of biomedical devices and are enclosed in the matrix of extracellular polymeric substances (EPSs). Biofilm formation is the cause of irreversible medical device infections and due to the high density of the bacteria within the biofilm, antibiotic resistant genes can transfer through conjugation, therefore the bacteria in the biofilm exhibit extraordinary resistance to antibiotics which can lead to chronic infection and inflammation [30,31].

Stages of biofilm formation

The classic model of biofilm development in Gram-negative bacteria (*Pseudomonas aeruginosa)* and Gram-positive bacteria (*S. aureus*) has four key stages leading to BAIs (Figure 2) These stages include 1) Adhesion or attachment of bacteria to the device surface, 2) formation of monolayer bacteria and micro-colony, 3) maturation of biofilm, and 4) dispersion or detachment of bacteria that can colonize to form further biofilms [24,25,27,28].

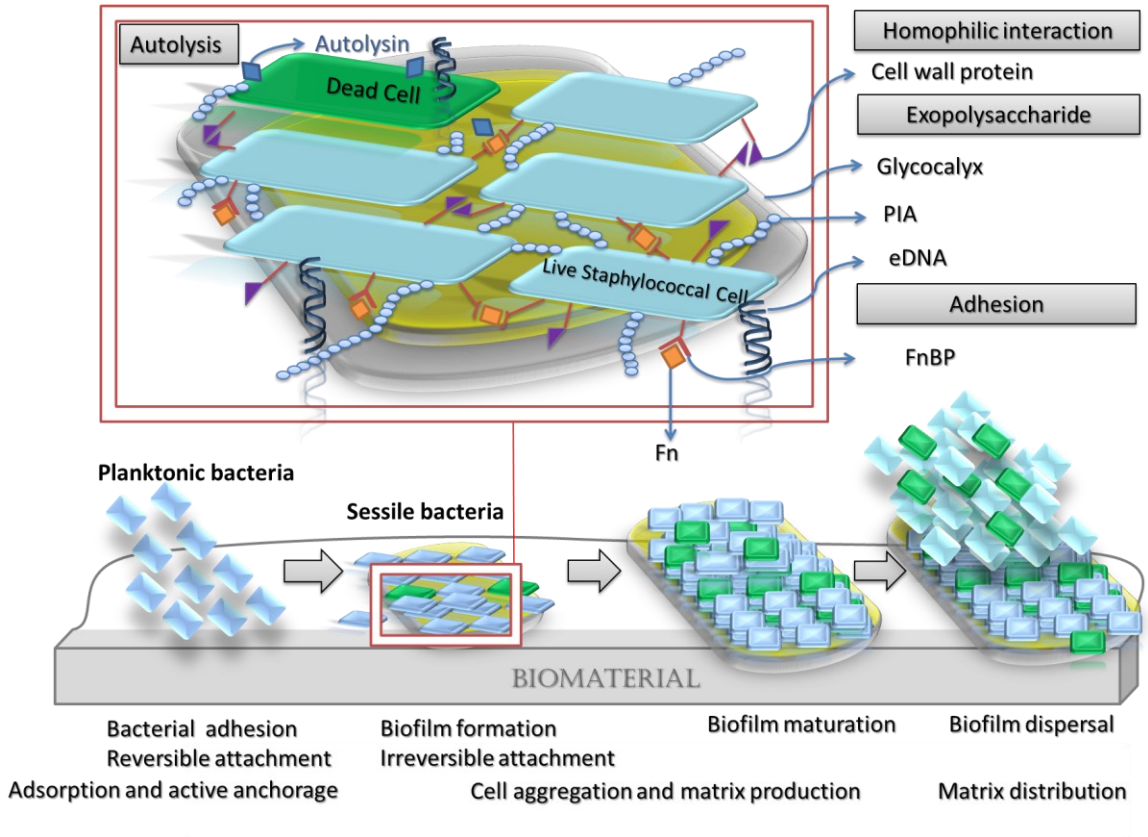

Figure 2 The attachment of planktonic bacteria attached to the surface is initially a reversible interaction. The stability of planktonic bacteria causes microcolony formation, followed by biofilm formation. In *S. aureus*, fibronectin (Fn) molecule interacts with fibronectin-binding protein (Fn BPs) and forms a bridge. Biofilm maturation begins with EPS production and bacterial aggregation, followed by the release of extracellular DNA (eDNA) and expression of polysaccharide intracellular adhesion (PIA). As the biofilm matures, water channels are formed and protease contribute to biofilm dispersal.

As biofilms develop, EPS is produced which assists with adhering bacteria together during maturation and later stage biofilm formation [32]. EPS is composed of extracellular DNA (eDNA), lipoteichoic acid (LTA), wall teichoic acid (WTA) and protein, in addition to exopolysaccharides. In *S. aureus* and *S. epidermidis*, the main polysaccharide component of the biofilm matrix is intercellular adhesion (PIA). Environmental stresses such as ethanol, heat, and osmolarity increases biofilm formation and PIA synthesis. PIA production is also increased in iron and nutrient limited conditions, and in the low oxygen environments. Stress conditions, especially in *S. aureus*, also correlate with a propensity for genetic mutation and horizontal gene transfer, leading to antibacterial resistance [33]. Biofilm formation is also impacted by physical stresses due to fluid flow, for example, shear stress in high in cerebrospinal fluid shunts and intravascular devices due to blood pressure. The eDNA possesses four critical roles; 1) gene transfer between bacterial cells, 2) supply of nutrients, 3) strengthening and stabilization of biofilm matrix, 4) modulation of the innate immune response. The release of eDNA from the biofilm cells causes stability of the mature biofilm, hence is an attractive target for future therapeutic coatings and diagnostic strategies. The cell envelope of the Gram-positive bacteria contains teichoic acid (TA)

that covalently bonds to peptidoglycan as WTA or to the cytoplasmic membrane as LTA. TAs play a significant role in adhesion of bacteria to biomaterials by binding to adsorbed fibronectin and assist with biofilm formation [31].

During biofilm formation, complex regulatory networks control bacterial cell interactions [34]. The alteration in gene expression in the bacterial cell is due to the colonization of bacteria. The key *S. aureus* genes involved in biomaterial colonization and BAI development are *icaADBC*, *agrBDCA* for the Agr quorum-sensing system, *altE* and *aap* encoding the accumulation-associated protein (AAP). The environment conditions, stresses and cell density impact bacterial responses and alter signaling systems via changes in gene expression [29,30].

Subsequent systemic infections can occur following colonization of biomaterials and this is largely due to biofilm dispersal and bacterial dissemination to the bloodstream. The enzymatic degradation of surfactant molecules and EPS, combined with the inhibition of matrix production all contribute to biofilm dispersal [30,35].

4. Implant-associated infections: prevalence and clinical complications

Bacterial contamination of prosthetic medical devices and implants can cause chronic life-threatening infections, characterized by device failure, high morbidity and mortality rates [36]. Infections can range from local abscesses to life-threatening infections [26,37]. Figure 3 shows the typical biofilm-mediated infections of skin and soft tissue, along with biomedical device-related infections. The route of infection can be attributed to the method of application, for example an infection may occur through a wound created to insert a peripheral vascular catheter or from insertion of a urinary catheter. Approximately 60% of healthcare-associated infections (HAIs) are due to bacterial contamination of medical devices and implants. Surgical site infections (SSIs) are the most common postoperative complication occurring in approximately 15% of clinical cases [29,36,38]. Resulting HAIs may include central line-associated bloodstream infections, ventilator-associated pneumonia, hospital-acquired pneumonia, SSIs, *Clostridium difficile* infections, and catheter-associated urinary tract infections. The main cause of bacterial HAIs infection is from the genus *Staphylococcus spp.* due to the ubiquity on the host skin. Whilst *S. epidermidis* has fewer virulence factors than *S. aureus*, the potential to develop biofilms partly explains its emergence as a major HAI pathogen [36,38–42] .

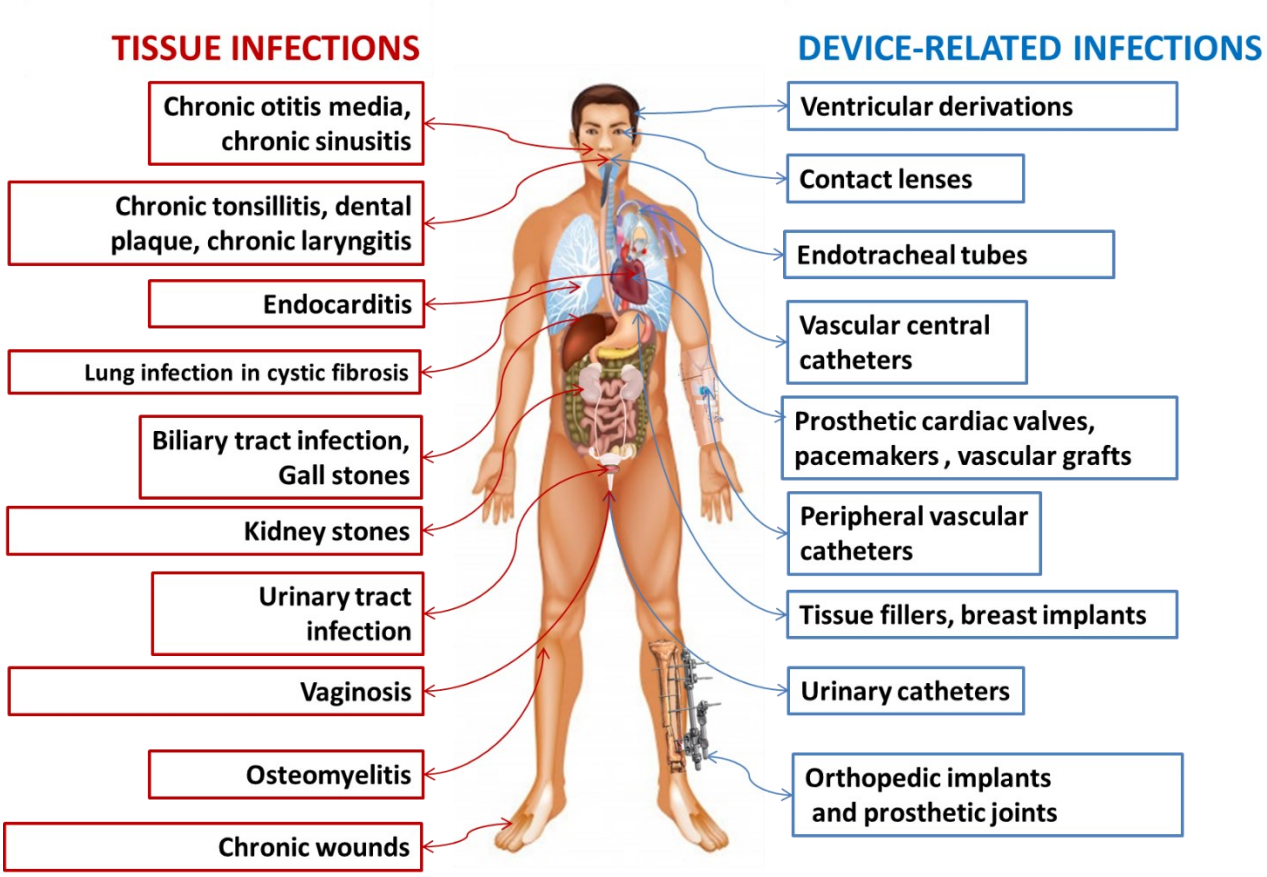

Figure 3 Typical bacterial infections of the skin and soft tissue, with respective biomedical devices.

The risk of BAIs and subsequent HAI is linked to the duration of the surgical procedure and is greater during the first six hours. Thereafter, the risk of implant colonization is never zero because of possible contamination by hematogenous routes or by contact with the external environment for devices with exposed apertures beyond the skin [43–46]. Several chronic infections are characterized by the inability to deliver chemotherpeutic agents, unable to sterilize some foci of infection, and the high risk of recurrence related to infections related to biofilm generation [47–49]. A wide range of medical devices are susceptible to bacterial colonization including intravascular, orthopedic, and urinary indwelling devices, cardiac pacemakers and heart valves, central venous catheters, artificial lenses, prosthetic joints, and vascular grafts. Both Gram-positive and Gram-negative bacteria are involved, with *S. aureus* being a major cause of infection [50,51]. Table 1 summarizes links between common biomedical devices, biomaterial and known bacterial pathogens, including infection rate and routes of transmission [7,38,52,53].

Table 1. Summary of links between common biomedical devices and biomaterial with known bacterial pathogens, including infection rate and routes of transmission

Biomedical device	Colonizing bacterial pathogen	Infection period	Infection rate	Biomaterials used	Routes of infection	Ref.
Central venous catheters	*S. epidermidis*, *S. aureus,* *C. albicans,* *P. aeruginosa,* *K. pneumoniae*	Within 10 days	3-14%	Silicone, Polytetrafluoroethylene (PTFE), polyurethane and Polyvinyl chloride	1. Through the wound created to insert the catheter 2. Through a contaminated catheter hub 3. Directly by bloodstream (BS) infection 4.Through contaminated infusate	[54–56]
Prosthetic heart valves	*S. aureus,* *Streptococcus* spp., *Candida* spp., *Enterococcus* spp.	Can be immediate causing surgical site infection	1-4%	PTFE, pyrolytic carbon	1. Can be from BS infections 2. Heart valve infections are common in patients with a repetitive history of endocarditis or frequent surgeries	[36,56,57]
Contact lenses and corneal implants	*S. epidermidis,* *E. coli,* *P. aeruginosa,* *S. aureus,* *Proteus* spp., *Serratia* spp., *Candida* spp.	Can develop immediately to several weeks	2.5-6%	Silicone hydrogel, Polymethylmethacrylate (PMMA)	1. Either by direct contact with lenses or via lens cases 2. It is also mediated by other risk factors such as age, gender, extended wear etc.	[56–61]
Dental implants	*Veillonella* spp., *F. nucleatum,* *A. naeslundii,* *Streptococcus* spp., *C. albicans,* *S. sanguinis,* *P. gingivalis,* *E. timidum,* *E. brachy,* *P. anerobicus*	Can develop immediately to 14 years	10-56%	Acrylic resin, titanium and its alloys, zirconia, silver and silver nanoparticles, ZnO	Dental plaque, dental caries and oral microbiome are the main sources of colonization	[56,57,60–68]
Orthopedic implants	*Staphylococcus* spp. (including MRSA) (20-50%), *Streptococcus* spp. *Enterococcus* spp. *P. mirabilis,* *E. coli,* *P. aeruginosa,* *P. acnes,*	Early infection: 3 months or less Late infection: 3-24 months Secondary infection: After 24 months	5-40%	HMWPE, PMMA, ceramics, cobalt, chromium, titanium, stainless steel and other metals and its alloys	1. At the time of implantation through direct inoculation or from airborne contamination of wound or device 2. From BS infections or adjacent focus of infection	[55,57,59,61,69–76]

Breast implants	*S. aureus,* *Enterococcus* spp., *S. epidermidis,* *P. acnes,* Diptheroids	20-280 days	1-35%	Silicone gel within silicone rubber envelope, inflatable saline	Skin microflora during surgery is the most common origin of infection, other routes include 1. Contaminated implant or surgical environment 2. Skin penetrating accidents 3. Local soft tissue infections 4. Breast trauma and seeding of implant from remote infections	[17,36,60,77–79]

5. Detection, prevention, and treatment

Challenge in the detection of implant-associated infections

The detection and treatment of biofilm-associated implant infections are challenging due to difficulty in preventing the growth of dormant bacteria in the biofilm and elimination of mature biofilms from the surface of the implant [80,81]. Traditional isolation methods such as conventional swabbing of infection sites have limited clinical relevance due to limited accessibility of the infected implant. Some studies suggest that the sonication fluid culture method is more sensitive than individual detection techniques, histology or pre-implant bacterial culture screening [82–86]. Classical culture techniques also rely on the growth potential of bacteria in defined culture medium, which is time consuming and less accurate. More rapid and sensitive culture independent techniques such as MALDI-TOF mass spectroscopy, Ibis PLEX- ID technology, next-generation sequencing are now indispensable technologies for epidemiological surveillance, especially for identification of HAIs and subsequent clinical management and progression, and for bacterial taxonomic/ phylogenetics research, but they are costly and insufficient validation in the management of patients [87–90].

Preventive strategies

Implanted medical devices are the major cause of HAIs. There are a series of interventions specifically designed to control, reduce and eliminate the risk of infections including, the geometry of the device which is especially important in intravascular devices, administration of preoperative antibiotics, procedure checklists, aseptic and sterile techniques, careful hemostasis, and chlorohexidine sponge dressing. Chlorhexidine sponge reduces the transfer of skin bacteria through an indwelling catheter into the blood vessel. The next intervention is nanoscale patterning of the medical device surface which can prevent bacterial adhesion and proliferation. Also, the incorporation of device materials with antimicrobial agents can prevent bacterial colonization on the implant surface. One of the major risk factors for infection of a surgical site in orthopedic and cardiac surgery can be prevented by the care management approaches, which are groups of evidenced-based interventions with maximum effective results. Currently, the main preventive strategy is the use of antimicrobial biomaterials [91–93].

Modifying the nano-topology and micro-topology are methods of reducing the possibility of microbial adhesion. Altering surface nano-topographies and/or coating biomedical surfaces with hydrophobic polymer brush systems or surfactants can confer antifouling, antimicrobial activity, anti-adhesive properties, and alterations in surface hydrophobicity [37,94]. Antimicrobial coating are either inhibitory or fatal to microbes, whereas antifouling agent inhibit the adhesion of microorganisms and proteins. The main mode of action for antibacterial potential is accomplished via 1) release of biocide or 2) the presence of contact-killing moieties near the surface. Antifouling approaches commonly employ one of several mechanisms to inhibit adhesion, include 1) low surface energy, 2) hydration/ steric repulsion, or 3) interactions of specific protein [95–97]. Ideal orthopedic implants should enhance the rapid adhesion to the host cell, improve tissue integration whilst impeding bacterial adhesion [98,99]. Figure 4 illustrates the possible strategies to prevent implant-tissue and implant colonization.

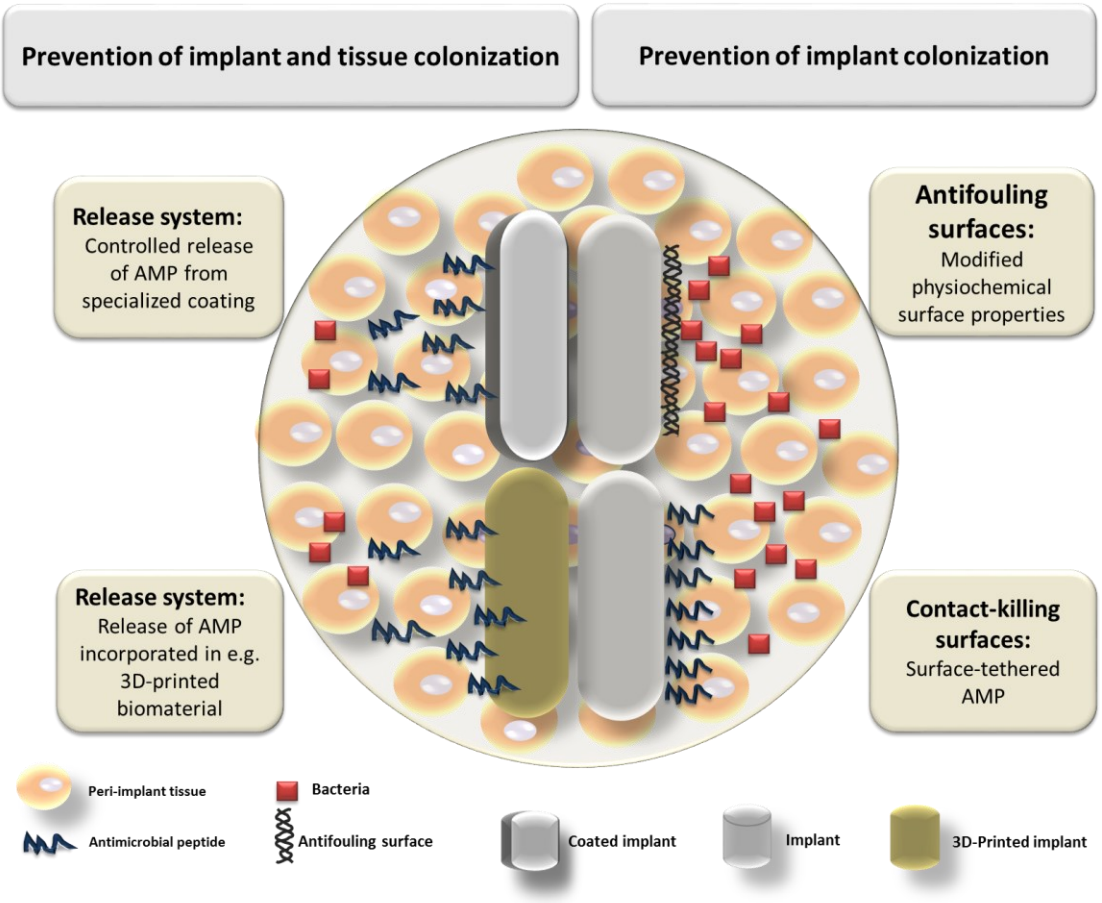

Figure 4 The antimicrobial strategies to inhibit biofilm formation on biomedical devices and colonization of the peri-implant tissue. The antimicrobial strategies to inhibit biomedical device colonization (right) include modification of physicochemical properties of the implant surface and using antifouling of the surface by immobilization of AMP for bacterial contact-killing. Release of incorporated AMP and inorganic nanomaterials (zinc, silver, and copper nanoparticles) in implants or release of these from surface coating are preventive antimicrobial strategies to inhibit tissue and biomedical device (left) colonization.

The main cause for the failure of an indwelling medical device is microbial contamination because of biofilm formation, blockage, and encrustation. With biofilms containing significant amounts of EPS, combined with the location of the device being largely inaccessible to the immune system, such infections represent a significant clinical challenge. There are various antimicrobial approaches to control or reduce indwelling BMIs using a combination and/or synergistic strategies [97,100–102] which are highlighted in Figure 5 and Table 2.

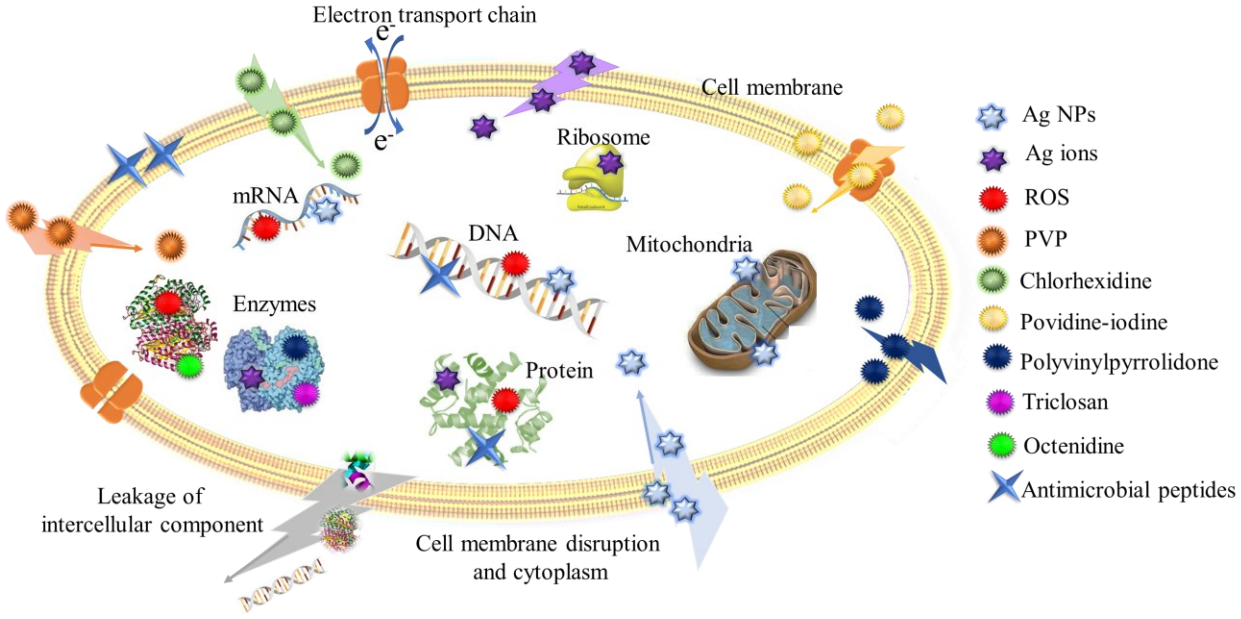

Figure 5 Antimicrobial mechanism of action of various materials, through different pathways which are shown to inhibit, denature, disrupt, and interfere with key cellular functions.

Table 2. Novel approaches to biomaterial modifications showing mechanisms of antimicrobial activity, coupled with associated medical devices.

Methods	Chemicals	Process/ mechanism	Medical device	Ref.
1. Antimicrobial approaches				
Incorporated inorganic chemicals	Silver/ silver nanoparticles (Ag NPs)	Ag ions (denature ribosomes and inhibit protein synthesis, interruption of electron transport chain) Generation of reactive oxygen species (ROS) (enzyme inhibition and disruption, DNA damage and repletion inhibition, protein denaturation and inhibition) Ag nanoparticles (direct disruption of cell wall and membrane)	Orthopedic materials and devices, central venous catheters, dental adhesive resins, orthodontic cement, and dental composites, wound-dressing, tissue scaffold	103–105

Copper nanoparticles (Cu NPs)	ROS generation through Fenton-type reaction causes oxidation of lipids and proteins. Cu NPs enter into bacterial membrane and attach with DNA and by cross-linking, interrupt the helical structure of DNA within and between the nucleic acid strands. Cu NPs can penetrate the intracellular environment and directly interact with oxidative organelles such as mitochondria. The increase in ROS generation, lead to inducing DNA damage and breaks and impact on gene expression. Cu^{2+} ions can chelate with biomolecules and inactivate functional protein. Cu^{2+} ion will also cause sulfhydryls (R–SH) depletion. The generated H_2O_2 molecules cause further generation of toxic hydroxyl radicals. Also, Cu^{2+} ions cause the displacement of iron from iron-sulfur clusters.	Prosthetic joint material, intensive care unit (ICU) rooms (pilot),	106–111
Zinc oxide nanoparticles (ZnO NPs)	ROS production using ultraviolet (UV). The reactive species from ROS products including OH^{-}, H_2O_2 and O^2 target cellular components, such as protein and DNA following entry into bacterial cells. Zn^{2+} ions significantly contribute to enzyme system disruption, amino acid metabolism disruption, and prevent bacterial active transport.	Mouth wash, orthopedic and dental implants	106,112–119
Gold nanoparticles (Au NPs)	Inhibition of ribosomal subunit and the cell wall perturbation, along with ATPase activity inhibition. Reduced ATPase activity decreases ATP levels whilst inhibition of ribosomal subunit prevents translation and protein synthesis. DNA interactions also contribute to Au antibacterial activity. Interactions of Au NPs with Gram-negative bacteria causes perturbation of the bacterial outer membrane and the generation of outer membrane vesicle. ROS generation stimulated by Au NPs target bacterial metabolism.	Coating material on medical-based surfaces. Silicone urinary catheter (antifouling agent)	106,120–123

Incorporated organic compounds	Chlorhexidine	Interaction with phosphatidylethanolamine and membrane cardiolipin, perturbation of the bilayer structure / disturbing normal arrangement leading to cell lysis	Peripherally inserted central venous catheters, urology catheter lubricants, needleless IV connectors, central venous catheters, mouthwashes, gargles, toothpaste, disinfectant and antiseptics	124–129
	Povidine-iodine (PVPeI)	Iodine enhances the antimicrobial potency of PVP through disruption of bacterial electron transport and oxidation of reactive moieties on the surface of the cell	Antiseptics and disinfectants	130–132
	Polyvinylpyrrolidone (PVP)	Disruption of the cell membrane and osmotic balance by increasing membrane permeability, impact the expression of genes involved in oxidative stress	Contact lenses, drug industry (tablets, capsule), paper-based cholesterol biosensor	
	Benzalkonium chloride (BAC)	Disruption of membranes by commencing autolysis and the leakage of intracellular constituents, a quaternary ammonium cation-based disinfectant	Antiseptic and disinfectant in pharmaceutical products, dental composites	133–136
	Triclosan	By targeting enoyl-[acyl-carrier protein] reductase causes inhibition of bacterial fatty acid synthesis	Antiseptic products, surgical gloves, implantable medical devices, toothpaste	137–139
	Octenidine	Interferes with the enzymatic systems, and disruption of the integrity of the bilayer cell envelope leading to the cytoplasmic leakage through the plasma membrane	Mouthwash, gutta-percha disinfectant, for biofilm inhibition on restorative materials, as a root canal medicament and root canal irritant, wound disinfectant	140,141
Antibiotic coatings	Gentamicin (GM)	Inhibition of ribosomal translocation	GM-loaded cement spacers for osteomyelitis and prosthetic joint-associated infection	142–144
	Rifampin	Prevention of DNA synthesis by targeting bacterial RNA polymerase	Coating of medical devices such as prosthetic heart valves	145–147

2. Surface modification and intrinsic surface antibacterial strategies				
Charged surfaces	Heparin	Reduces pathogen adhesion due to inducing increment surface hydrophilicity leads to a hydrated interface	Cardiopulmonary bypass devices, hemodialysis catheters, Coronary stents, heparin coating kit, coronary stents, vascular grafts	[148–151]
	Poly(ethylene glycol) (PEG)	Reduces microbial adhesion by inducing increment surface	Hydrophilic linear polymer used as an antifouling coating on catheters, hydrogel or as a pore former in dialysis membrane	[152–155]
Biological and naturally derived strategies	Antimicrobial peptides (AMPs)	Disruption of cell membrane synthesis, inhibition of protein, and nucleic acid synthesis by the interaction of the cationic molecule with negatively charged components in the bacterial cell envelope	Urinary catheters, central venous catheters	[156–161]
	Chitosan [poly-(b-1/4)-2-amino-2-deoxy-D-glucopyranose]	Bactericidal effect by binding the teichoic acids within the bacterial cell wall and prevents cell division	Vaccine delivery, tissue regeneration, 3D scaffolding, contact lens	[162–166]
	Lactobacillus spp derived biosurfactants	Reduces interfacial tension and surface tension, decrease microbial adhesion to the surface and prevent biofilm proliferation and formation	Silicone tube and disk	[167–170]

Conventional therapeutic strategies

Conservative approaches rely on implant retention and debridement can be considered only for infected implant that are detected after implantation within four weeks [171–173]. The treatment in late implant infections, consists of two stages, a) implant exchange, b) permanent resection arthroplasty, and in case of treatment failure or risk of relapse, the next procedure is amputation. The two-step revision surgery of chronic infections includes debridement of all nonviable tissues, resection of infected medical devices with or without temporary antibiotic incorporated cement spacer, and the next step is the replacement of the prostatic implant after eradication of the infection. In one-step revision surgery following chronic infection, the replacement of the implant is performed in the same surgical procedure after resection of the infected site [174–177]. The most important antibiotic against staphylococcal biofilm infection is rifampicin which diffuses well within the bacterial biofilm, host cell, bone tissue and it prevents DNA-dependent RNA synthesis independently of bacterial growth and metabolic activity, therefore is very effective against bacterial biofilms. Rifampicin can be used with other antimicrobials due to the high risk of resistance emergence [147,178–180].

Phage-based nanomaterial strategies: an alternative to conventional therapeutic strategies

Recent developments in nanotechnology permit manipulation and generation of materials with molecular-level control. In the novel emerging field of bionanomedicine, controlling the biological, chemical, and physical features of ingredients is important. Amongst other biological building blocks, viruses are a potential nanosize material that can be precisely functionalized [181,182]. Bacteriophages (phages) are viruses that infect bacteria and have no cytotoxic effects on human cells, meaning they exhibit differential toxicity, which is a highly desirable property for use within implanted biomaterials. They can have a broad range of bacterial hosts or a narrow spectrum of activity by infecting several species only or even a single bacterial strain [183]. Whole phage particles and phage proteins are being employed in the advancing new functional nanomaterials with nanosize properties [184]. Bacteriophage-functionalized bioactive surfaces are functional substances that can be employed as antibacterial/ antifouling surfaces in biomedical uses (*e.g.*, indwelling medical devices (implants, stents, catheters) and wound dressings) [183]. The ability to target and destroy bacteria is a key principle for employing phages in antimicrobial chemotherapy and for bacterial diagnosis [185]. There are recent examples of combining phages with natural polymers (e.g., alginates, chitosan, collagen fibers), and synthetic polymers and even in the form of electrospun fibrous mats [185]. Recently, phage therapy has been the subject of renewed interest due to the emergence of antimicrobial resistance [186].

Bacteriophages propagate at the expense of bacteria. The genetic materials of the phages are released into the cytoplasm after attachment to the bacterial surface. The host cell mechanism causes the development of phage compartments and new phage assembly inside the infected bacteria. bacterial lysis occurs due to the generation of new phage and led to the progeny of phage that subsequently starts infection cycles. Phages are known to choose among the mixture of bacteria populations. Hence, bacteriophage lytic cycle disturbance can cause to establish an alternative but selective method for pathogenic bacteria targeting over host commensal bacteria. (Figure 6).

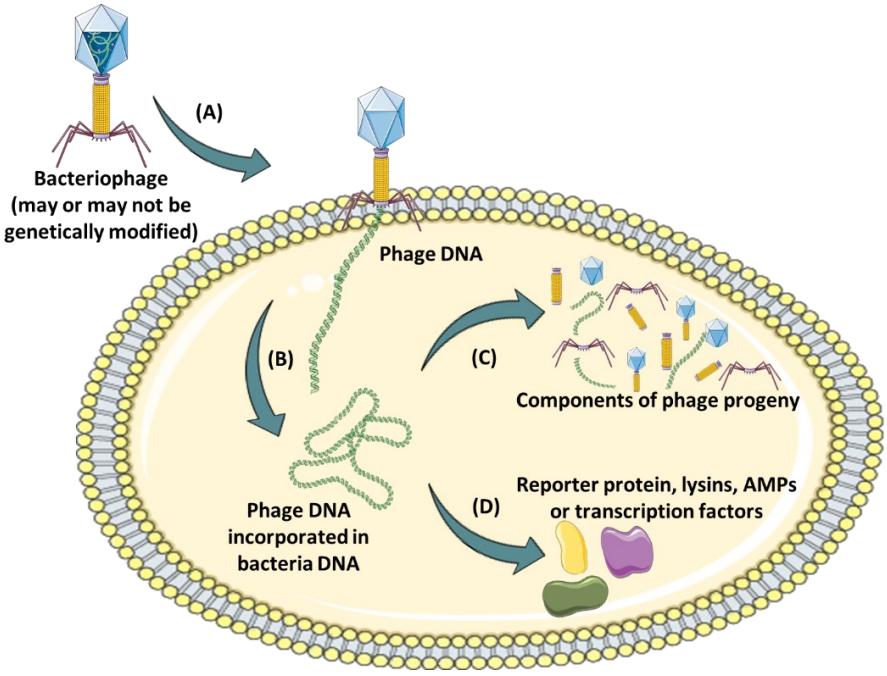

Figure 6 Phage-based nanomaterial strategies. (A) Genetically modified or natural phages will selectively target bacteria. (B) The phage genome will be integrated into the bacterial genome, and replication will commence using host machinery. (C) Translation into progeny phage particles, which will assemble and lyse the cell. (D) Expression of reporter proteins, lysins, toxins, and AMPs to destroy the bacteria.

6. Perspectives for the future development of medical devices

As implanted biomedical devices are the number one cause of HAIs, there are specific proposed interventions to control or eradicate infection. Identifying the clinical nature of device infections and associated pathogenesis provides a framework for understanding various potential treatment and prevention strategies. Fig. 6 illustrates the treatments to eliminate or control infection. Fig. 6A represents the procedural modification to prevent and reduce infection rate in targeted point include procedure checklist, sterile techniques, perioperative antibiotics, careful hemostasis, and chlorhexedeine sponge dressings[36,38,187–190]. Fig. 6B display that the geometry of medical devices can vary the possibility of infection, which is essential for intravascular devices. The proteins, cells (bacteria or host) are transferred and deposited on the surface of medical devices through Brownian diffusion and blood flow which is related to medical device geometry [191,192]. Different studies demonstrate that device geometry of ventricular assist devices, heart valve, oxygenators, and dialysis catheter decrease thrombosis and platelet deposition [193,194]. The polymer coating is an efficient strategy that attempts to alter surface physiochemical features of the surface to inhibit bacterial attachment, or with bactericidal properties destroy the bacteria (Fig. 7C). Incorporation of antimicrobial agents (eg. chlorohexidine, silver, minocycline, and rifampin) into the medical devices elute from the surface and demolish the bacteria that contact with (Fig. D). The life span of these surfaces is limited because of the diminution of antimicrobial agents from continuous pacification or elution by host protein [38]. Fig. 7D illustrates that surface topography can control cell attachment and proliferation. [196,197]. The surgical site risk factors and the regimen to control multidrug-resistant strains of bacteria such as methicillin-resistant *S. aureus* (MRSA) infections have been well documented. The "care bundle" approach can significantly reduce major orthopedic and cardiac surgery infections. Care bundles are series of evidence-based interventions with the highest outcome benefit if applied together. The development of antibacterial biomaterials currently represents a main preventative strategy [38].

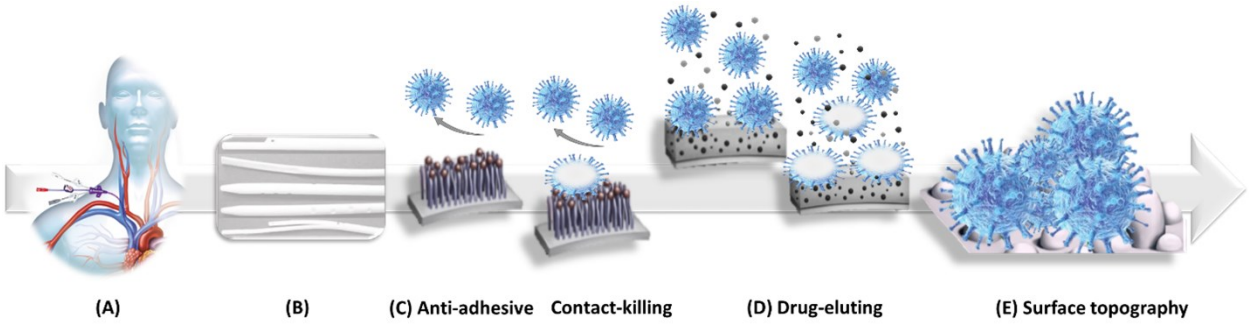

Figure 7 Prophylactic antimicrobial approaches to preventing implantable biomedical device infections. (A) Decreased transport of skin bacteria to the bloodstream along the catheter by using chlorhexidine sponge at the site of insertion of a triple lumen central venous catheter. (B) Blood flow patterns can be altered by using dialysis catheters with various geometries, therefore

preventing bacterial cell and/or host cell attachment to the surface. (C) Specific chemical end groups on the surface of the polymer can inhibit attachment, or have antimicrobial properties upon contact. (D) Bacteria near the medical device can be eliminated by impregnation with antimicrobial substances. (E) Bacterial adhesion and proliferation can be altered by nanoscale patterning of the biomaterial surface.

One of the main challenges in the medical field is the treatment and prevention of BAIs, particularly biofilm formation and intracellular multidrug-resistant bacteria which cause HAIs. For significant reductions in HAIs, a number of factors should be simultaneously investigated and employed. These consist of extra research and advancement in antimicrobial encapsulated and release technology for biomedical device production, rigorous use of aseptic methods with the continuous training programs, research and education for related healthcare professionals. One of the major challenges faced by the medical device industry is the emergence of multidrug-resistant bacterial infections, which are largely untreatable with conventional methods. The prevention of pathogenic biofilm formation is the main strategy for the eradication/reduction in HAIs. Some of the most promising nanotechnology and biotechnology developments include the use of phage incorporated into medical devices as antimicrobial chemotherapeutic materials. Recent advances in genome sequencing technology, molecular cloning and genetic engineering could permit the generation of phage with enhanced properties, such as bacterial strain specificity, for incorporation into slow releasing biomaterials. Finally, consideration of cost verses benefits to healthcare should also be considered when choosing biomaterials for use within implanted devices.

7. Conclusion

Biomedical device infections are a serious concern to healthcare and represent some of the most challenging infections for medical intervention. Biomedical implants can affect host immune defenses and cause the growth of bacteria, persister cell generation, biofilm formation, osteoblast invasion, immune evasion, and ultimately antibacterial resistance. Hence, the inhibition of biomedical device infections is critical and it begins with the understanding of several risk factors in pre-operation, post-operation, and the nature of the operation. The concentration of antibiotics is significantly important due to the stimulation of persister cell formation. Additionally, invasion of host cells causes the failure of antibacterial treatment. The permeability of host cells determines the efficacy of antibiotics to prevent or treat the infection. Further research on antimicrobial strategies for enhancing drug permeability into the host cells in dormant bacteria is required. Cell-penetrating cationic polymers with antimicrobial potential against intracellular bacteria seem promising. The research on novel anti-infective implant biomaterials and innovative therapeutic strategies, such as the use of phage, is promising to prevent, treat, and detect biomedical devices infection. The nanoscience strategies largely focus on surface modification of biomedical implants by functional decoration and fabrication of "smart surfaces" to permit the generation and release of antimicrobial agents. The efficiency, durability, biocompatibility, and mechanical stability of applied antimicrobial nanomaterials in biomedical devices are key factors in the selection of nanostructured materials.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Mina Zare and Mohammad Zare researched the data for the article contributed substantially to the discussion of the content and wrote, reviewed, and edited the manuscript before submission. Jonathan A. Butler contributed in revision of the manuscript.
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Ethics declarations

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References

(1) Ghasemi-Mobarakeh, L.; Kolahreez, D.; Ramakrishna, S.; Williams, D. Key Terminology in Biomaterials and Biocompatibility. *Curr. Opin. Biomed. Eng.* **2019**, *10*, 45–50.

(2) Chen, F. M.; Liu, X. Advancing Biomaterials of Human Origin for Tissue Engineering. *Prog. Polym. Sci.* **2016**, *53*, 86–168.

(3) Martins, N.; Rodrigues, C. F. Biomaterial-Related Infections. *J. Clin. Med.* **2020**, *9* (3),

722.

(4) *Medical Device Accessories-Describing Accessories and Classification Pathways Guidance for Industry and Food and Drug Administration Staff*; 2017.

(5) Medical Device Accessories | FDA https://www.fda.gov/medical-devices/classify-your-medical-device/medical-device-accessories (accessed Oct 29, 2020).

(6) Batoni, G.; Maisetta, G.; Esin, S. Antimicrobial Peptides and Their Interaction with Biofilms of Medically Relevant Bacteria. *Biochim. Biophys. Acta - Biomembr.* **2016**, *1858* (5), 1044–1060.

(7) Khatoon, Z.; McTiernan, C. D.; Suuronen, E. J.; Mah, T. F.; Alarcon, E. I. Bacterial Biofilm Formation on Implantable Devices and Approaches to Its Treatment and Prevention. *Heliyon* **2018**, *4* (12), e01067.

(8) Frazão, L. P.; Vieira de Castro, J.; Neves, N. M. In Vivo Evaluation of the Biocompatibility of Biomaterial Device. In *Advances in Experimental Medicine and Biology*; Springer, 2020; Vol. 1250, pp 109–124.

(9) Anderson, J. M. Future Challenges in the in Vitro and in Vivo Evaluation of Biomaterial Biocompatibility. *Regen. Biomater.* **2016**, *3* (2), 73–77.

(10) Masters, E. A.; Trombetta, R. P.; de Mesy Bentley, K. L.; Boyce, B. F.; Gill, A. L.; Gill, S. R.; Nishitani, K.; Ishikawa, M.; Morita, Y.; Ito, H.; Bello-Irizarry, S. N.; Ninomiya, M.; Brodell, J. D.; Lee, C. C.; Hao, S. P.; Oh, I.; Xie, C.; Awad, H. A.; Daiss, J. L.; Owen, J. R.; Kates, S. L.; Schwarz, E. M.; Muthukrishnan, G. Evolving Concepts in Bone Infection: Redefining "Biofilm", "Acute vs. Chronic Osteomyelitis", "the Immune Proteome" and "Local Antibiotic Therapy." *Bone Res.* **2019**, *7* (1), 1–18.

(11) Food, U. S. *Biological Responses to Metal Implants*; 2019.

(12) Mariani, E.; Lisignoli, G.; Borzì, R. M.; Pulsatelli, L. Biomaterials: Foreign Bodies or Tuners for the Immune Response? *Int. J. Mol. Sci.* **2019**, *20* (3), 636.

(13) Gupta, P.; Sarkar, S.; Das, B.; Bhattacharjee, S.; Tribedi, P. Biofilm, Pathogenesis and Prevention—a Journey to Break the Wall: A Review. *Arch. Microbiol.* **2016**, *198* (1), 1–15.

(14) Dang, H.; Lovell, C. R. Microbial Surface Colonization and Biofilm Development in Marine Environments. *Microbiol. Mol. Biol. Rev.* **2016**, *80* (1), 91–138.

(15) Kimkes, T. E. P.; Heinemann, M. How Bacteria Recognise and Respond to Surface Contact. *FEMS Microbiol. Rev.* **2019**, *44* (1), 106–122.

(16) Muhammad, M. H.; Idris, A. L.; Fan, X.; Guo, Y.; Yu, Y.; Jin, X.; Qiu, J.; Guan, X.; Huang, T. Beyond Risk: Bacterial Biofilms and Their Regulating Approaches. *Front. Microbiol.* **2020**, *11*.

(17) Arciola, C. R.; Campoccia, D.; Montanaro, L. Implant Infections: Adhesion, Biofilm Formation and Immune Evasion. *Nat. Rev. Microbiol.* **2018**, *16* (7), 397–409.

(18) Ahmed, W.; Zhai, Z.; Gao, C. Adaptive Antibacterial Biomaterial Surfaces and Their Applications. *Mater. Today Bio* **2019**, *2*.

(19) Arias, S. L.; Devorkin, J.; Civantos, A.; Paul Allain, J. E. Coli Adhesion and Biofilm Formation on Polydimethylsiloxane Are Independent of Substrate Stiffness. *bioRxiv* **2020**,

2020.01.15.907956.

(20) Olmo, J. A. Del; Ruiz-Rubio, L.; Pérez-Alvarez, L.; Sáez-Martínez, V.; Vilas-Vilela, J. L. Antibacterial Coatings for Improving the Performance of Biomaterials. *Coatings* **2020**, *10* (2), 139.

(21) Gebreyohannes, G.; Nyerere, A.; Bii, C.; Sbhatu, D. B. Challenges of Intervention, Treatment, and Antibiotic Resistance of Biofilm-Forming Microorganisms. *Heliyon* **2019**, *5* (8), e02192–e02192.

(22) Beitelshees, M.; Hill, A.; Jones, C. H.; Pfeifer, B. A. Phenotypic Variation during Biofilm Formation: Implications for Anti-Biofilm Therapeutic Design. *Materials (Basel).* **2018**, *11* (7), 1086.

(23) Banerjee, D.; Shivapriya, P. M.; Gautam, P. K.; Misra, K.; Sahoo, A. K.; Samanta, S. K. A Review on Basic Biology of Bacterial Biofilm Infections and Their Treatments by Nanotechnology-Based Approaches. *Proc. Natl. Acad. Sci. India Sect. B - Biol. Sci.* **2020**, *90* (2), 243–259.

(24) Obolski, U.; Hadany, L. Implications of Stress-Induced Genetic Variation for Minimizing Multidrug Resistance in Bacteria. *BMC Med.* **2012**, *10* (1), 89.

(25) Heilmann, C.; Hussain, M.; Peters, G.; Götz, F. Evidence for Autolysin-Mediated Primary Attachment of Staphylococcus Epidermidis to a Polystyrene Surface. *Mol. Microbiol.* **1997**, *24* (5), 1013–1024.

(26) Alam, F.; Kumar, S.; Varadarajan, K. M. Quantification of Adhesion Force of Bacteria on the Surface of Biomaterials: Techniques and Assays. *ACS Biomater. Sci. Eng.* **2019**, *5* (5), 2093–2110.

(27) Houston, P.; Rowe, S. E.; Pozzi, C.; Waters, E. M.; O'Gara, J. P. Essential Role for the Major Autolysin in the Fibronectin-Binding Protein-Mediated Staphylococcus Aureus Biofilm Phenotype. *Infect. Immun.* **2011**, *79* (3), 1153–1165.

(28) Flemming, H. C.; Wingender, J.; Szewzyk, U.; Steinberg, P.; Rice, S. A.; Kjelleberg, S. Biofilms: An Emergent Form of Bacterial Life. *Nat. Rev. Microbiol.* **2016**, *14* (9), 563–575.

(29) Vestby, L. K.; Grønseth, T.; Simm, R.; Nesse, L. L. Bacterial Biofilm and Its Role in the Pathogenesis of Disease. *Antibiotics* **2020**, *9* (2), 59.

(30) Schaeffer, C. R.; Hoang, T.-M. N.; Sudbeck, C. M.; Alawi, M.; Tolo, I. E.; Robinson, D. A.; Horswill, A. R.; Rohde, H.; Fey, P. D. Versatility of Biofilm Matrix Molecules in Staphylococcus Epidermidis Clinical Isolates and Importance of Polysaccharide Intercellular Adhesin Expression during High Shear Stress. *mSphere* **2016**, *1* (5), e00165-16.

(31) Montanaro, L.; Poggi, A.; Visai, L.; Ravaioli, S.; Campoccia, D.; Speziale, P.; Arciola, C. R. Extracellular DNA in Biofilms. *Int. J. Artif. Organs* **2011**, *34* (9), 824–831.

(32) Paharik, A. E.; Horswill, A. R. The Staphylococcal Biofilm: Adhesins, Regulation, and Host Response. *Microbiol. Spectr.* **2016**, *4* (2), VMBF-0022-2015.

(33) Roberts, A. P.; Kreth, J. The Impact of Horizontal Gene Transfer on the Adaptive Ability of the Human Oral Microbiome. *Front. Cell. Infect. Microbiol.* **2014**, *4* (SEP).

(34) Thurlow, L. R.; Hanke, M. L.; Fritz, T.; Angle, A.; Aldrich, A.; Williams, S. H.; Engebretsen, I. L.; Bayles, K. W.; Horswill, A. R.; Kielian, T. Staphylococcus Aureus Biofilms Prevent Macrophage Phagocytosis and Attenuate Inflammation In Vivo. *J. Immunol.* **2011**, *186* (11), 6585–6596.

(35) Arciola, C. R.; Campoccia, D.; Ravaioli, S.; Montanaro, L. Polysaccharide Intercellular Adhesin in Biofilm: Structural and Regulatory Aspects. *Front. Cell. Infect. Microbiol.* **2015**, *5* (FEB).

(36) Darouiche, R. O. Treatment of Infections Associated with Surgical Implants. *N. Engl. J. Med.* **2004**, *350* (14), 1422–1429.

(37) Khalid, S.; Gao, A.; Wang, G.; Chu, P. K.; Wang, H. Tuning Surface Topographies on Biomaterials to Control Bacterial Infection. *Biomater. Sci.* **2020**, *8*, 6840–6857.

(38) Van Epps, J. S.; Younger, J. G. Implantable Device-Related Infection. *Shock* **2016**, *46* (6), 597–608.

(39) *WHO Guidelines on Core Components of Infection Prevention and Control Programmes at the National and Health Care Facility Level Web Appendix I Core Elements of Effective Infection Prevention and Control Programmes in Acute Health Care Facilities: A System*; 2017.

(40) Khan, H. A.; Baig, F. K.; Mehboob, R. Nosocomial Infections: Epidemiology, Prevention, Control and Surveillance. *Asian Pac. J. Trop. Biomed.* **2017**, *7* (5), 478–482.

(41) Monegro, A. F.; Muppidi, V.; Regunath, H. *Hospital Acquired Infections*; StatPearls Publishing, 2020.

(42) Types of Healthcare-associated Infections | HAI | CDC https://www.cdc.gov/hai/infectiontypes.html (accessed Oct 30, 2020).

(43) Seebach, E.; Kubatzky, K. F. Chronic Implant-Related Bone Infections-Can Immune Modulation Be a Therapeutic Strategy? *Front. Immunol.* **2019**, *10*, 1724.

(44) Romanò, C. L.; Scarponi, S.; Gallazzi, E.; Romanò, D.; Drago, L. Antibacterial Coating of Implants in Orthopaedics and Trauma: A Classification Proposal in an Evolving Panorama. *J. Orthop. Surg. Res.* **2015**, *10*, 157.

(45) Hickok, N. J.; Shapiro, I. M. Immobilized Antibiotics to Prevent Orthopaedic Implant Infections. *Adv. Drug Deliv. Rev.* **2012**, *64* (12), 1165–1176.

(46) Davidson, D. J.; Spratt, D.; Liddle, A. D. Implant Materials and Prosthetic Joint Infection: The Battle with the Biofilm. *EFORT Open Rev.* **2019**, *4* (11), 633–639.

(47) Global Guidelines for the Prevention of Surgical Site Infection-WHO http://www.who.int (accessed Oct 30, 2020).

(48) Ribeiro, M.; Monteiro, F. J.; Ferraz, M. P. Infection of Orthopedic Implants with Emphasis on Bacterial Adhesion Process and Techniques Used in Studying Bacterial-Material Interactions. *Biomatter* **2012**, *2* (4), 176–194.

(49) Healthcare-associated infections | HAI | CDC https://www.cdc.gov/hai/index.html (accessed Oct 30, 2020).

(50) Savage, V. J.; Chopra, I.; O'Neill, A. J. Staphylococcus Aureus Biofilms Promote Horizontal Transfer of Antibiotic Resistance. *Antimicrob. Agents Chemother.* **2013**, *57*

(4), 1968–1970.

(51) Moormeier, D. E.; Bayles, K. W. Staphylococcus Aureus Biofilm: A Complex Developmental Organism. *Mol. Microbiol.* **2017**, *104* (3), 365–376.

(52) Trampuz, A.; Zimmerli, W. Diagnosis and Treatment of Implant-Associated Septic Arthritis and Osteomyelitis. *Curr. Infect. Dis. Rep.* **2008**, *10* (5), 394–403.

(53) Zimmerli, W.; Trampuz, A. Implant-Associated Infection. In *Biofilm Infections*; Springer New York, 2011; pp 69–90.

(54) Zhang, L.; Gowardman, J.; Rickard, C. M. Impact of Microbial Attachment on Intravascular Catheter-Related Infections. *Int. J. Antimicrob. Agents* **2011**, *38* (1), 9–15.

(55) Guggenbichler, J. P.; Assadian, O.; Boeswald, M.; Kramer, A. Incidence and Clinical Implication of Nosocomial Infections Associated with Implantable Biomaterials - Catheters, Ventilator-Associated Pneumonia, Urinary Tract Infections. *GMS Krankenhaushygiene Interdiszip.* **2011**, *6* (1), Doc18–Doc18.

(56) Kokare, C. R.; Chakraborty, S.; Khopade, A. N.; Mahadik, K. R. Biofilm: Importance and Applications. *Indian J. Biotechnol.* **2009**, *8*, 159–168.

(57) Rodrigues, L.; Banat, I. M.; Teixeira, J.; Oliveira, R. Strategies for the Prevention of Microbial Biofilm Formation on Silicone Rubber Voice Prostheses. *J. Biomed. Mater. Res. - Part B Appl. Biomater.* **2007**, *81* (2), 358–370.

(58) Stoica, P.; Chifiriuc, M. C.; Rapa, M.; Lazăr, V. Overview of Biofilm-Related Problems in Medical Devices. In *Biofilms and Implantable Medical Devices: Infection and Control*; Elsevier Inc., 2017; pp 3–23.

(59) Steele, K. R.; Szczotka-flynn, L.; Szczotka-Flynn, L. Epidemiology of Contact Lens-Induced Infiltrates: An Updated Review. *Clin. Exp. Optom.* **2017**, *100* (5), 473–481.

(60) Bryers, J. D. Medical Biofilms. *Biotechnol. Bioeng.* **2008**, *100* (1), 1–18.

(61) Darouiche, R. O. Device-Associated Infections: A Macroproblem That Starts with Microadherence. *Clin. Infect. Dis.* **2001**, *33* (9), 1567–1572.

(62) Rimondini, L.; Cochis, A.; Varoni, E.; Azzimonti, B.; Carrassi, A. Biofilm Formation on Implants and Prosthetic Dental Materials. In *Handbook of Bioceramics and Biocomposites*; Springer International Publishing: Cham, 2016; pp 991–1027.

(63) Al-Ahmad, A.; Wiedmann-Al-Ahmad, M.; Faust, J.; Bächle, M.; Follo, M.; Wolkewitz, M.; Hannig, C.; Hellwig, E.; Carvalho, C.; Kohal, R. Biofilm Formation and Composition on Different Implant Materials in Vivo. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2010**, *95B* (1), 101–109.

(64) Laosuwan, K.; Epasinghe, D. J.; Wu, Z.; Leung, W. K.; Green, D. W.; Jung, H. S. Comparison of Biofilm Formation and Migration of Streptococcus Mutans on Tooth Roots and Titanium Miniscrews. *Clin. Exp. Dent. Res.* **2018**, *4* (2), 40–47.

(65) Gökmenoglu, C.; Kara, N. B.; Beldüz, M.; Kamburoğlu, A.; Tosun, I.; Sadik, E.; Kara, C. Evaluation of Candida Albicans Biofilm Formation on Various Parts of Implant Material Surfaces. *Niger. J. Clin. Pract.* **2018**, *21* (1), 33–37.

(66) Roehling, S.; Astasov-Frauenhoffer, M.; Hauser-Gerspach, I.; Braissant, O.; Woelfler, H.; Waltimo, T.; Kniha, H.; Gahlert, M. In Vitro Biofilm Formation on Titanium and Zirconia

Implant Surfaces. *J. Periodontol.* **2017**, *88* (3), 298–307.

(67) Frisch, E.; Ziebolz, D.; Vach, K.; Ratka-Krüger, P. Supportive Post-Implant Therapy: Patient Compliance Rates and Impacting Factors: 3-Year Follow-Up. *J. Clin. Periodontol.* **2014**, *41* (10), 1007–1014.

(68) Shah, S. R.; Tatara, A. M.; D'Souza, R. N.; Mikos, A. G.; Kasper, F. K. Evolving Strategies for Preventing Biofilm on Implantable Materials. *Mater. Today* **2013**, *16* (5), 177–182.

(69) Chukwuanukwu, T.; Ikeanyi, U.; Chukwuka, C. Risk Factors for Surgical Site Infections Following Clean Orthopaedic Operations. *Niger. J. Clin. Pract.* **2013**, *16* (4), 443.

(70) Nickinson, R. S. J.; Board, T. N.; Gambhir, A. K.; Porter, M. L.; Kay, P. R. The Microbiology of the Infected Knee Arthroplasty. *Int. Orthop.* **2010**, *34* (4), 505–510.

(71) Glage, S.; Paret, S.; Winkel, A.; Stiesch, M.; Bleich, A.; Krauss, J. K.; Schwabe, K. A New Model for Biofilm Formation and Inflammatory Tissue Reaction: Intraoperative Infection of a Cranial Implant with Staphylococcus Aureus in Rats. *Acta Neurochir. (Wien).* **2017**, *159* (9), 1747–1756.

(72) Chu, C.-B.; Zeng, H.; Shen, D.-X.; Wang, H.; Wang, J.-F.; Cui, F.-Z. A New Rabbit Model of Implant-Related Biofilm Infection: Development and Evaluation. *Front. Mater. Sci.* **2016**, *10* (1), 80–89.

(73) Johansson, L.; Hailer, N. P.; Rahme, H. High Incidence of Periprosthetic Joint Infection with Propionibacterium Acnes after the Use of a Stemless Shoulder Prosthesis with Metaphyseal Screw Fixation - a Retrospective Cohort Study of 241 Patients Propionibacter Infections after Eclipse TSA. *BMC Musculoskelet. Disord.* **2017**, *18* (1), 203.

(74) Sabaté Brescó, M.; Harris, L. G.; Thompson, K.; Stanic, B.; Morgenstern, M.; O'Mahony, L.; Richards, R. G.; Moriarty, T. F. Pathogenic Mechanisms and Host Interactions in Staphylococcus Epidermidis Device-Related Infection. *Front. Microbiol.* **2017**, *8* (AUG).

(75) Ribeiro, M.; Monteiro, F. J.; Ferraz, M. P. Infection of Orthopedic Implants with Emphasis on Bacterial Adhesion Process and Techniques Used in Studying Bacterial-Material Interactions. *Biomatter* **2012**, *2* (4), 176–194.

(76) Arciola, C. R.; Campoccia, D.; Montanaro, L. Implant Infections: Adhesion, Biofilm Formation and Immune Evasion. *Nat. Rev. Microbiol.* **2018**, *16* (7), 397–409.

(77) Okuda, K.; Nagahori, R.; Yamada, S.; Sugimoto, S.; Sato, C.; Sato, M.; Iwase, T.; Hashimoto, K.; Mizunoe, Y. The Composition and Structure of Biofilms Developed by Propionibacterium Acnes Isolated from Cardiac Pacemaker Devices. *Front. Microbiol.* **2018**, *9* (FEB).

(78) Donelli, G. *Biofilm-Based Healthcare-Associated Infections*; Donelli, G., Ed.; Advances in Experimental Medicine and Biology; Springer International Publishing: Cham, 2015; Vol. 831.

(79) BASILE, A.; BASILE, F.; BASILE, A. Late Infection Following Breast Augmentation with Textured Silicone Gel–Filled Implants. *Aesthetic Surg. J.* **2005**, *25* (3), 249–254.

(80) McConoughey, S. J.; Howlin, R.; Granger, J. F.; Manring, M. M.; Calhoun, J. H.; Shirtliff,

M.; Kathju, S.; Stoodley, P. Biofilms in Periprosthetic Orthopedic Infections. *Future Microbiol.* **2014**, *9* (8), 987–1007.

(81) Kavanagh, N.; Ryan, E. J.; Widaa, A.; Sexton, G.; Fennell, J.; O'Rourke, S.; Cahill, K. C.; Kearney, C. J.; O'Brien, F. J.; Kerrigan, S. W. Staphylococcal Osteomyelitis: Disease Progression, Treatment Challenges, and Future Directions. *Clin. Microbiol. Rev.* **2018**, *31* (2), e00084-17.

(82) Drago; Clerici; Morelli; Ashok; Benzakour; Bozhkova; Alizadeh; del Sel; Sharma; Peel; Mattina; Romanò. The World Association against Infection in Orthopaedics and Trauma (WAIOT) Procedures for Microbiological Sampling and Processing for Periprosthetic Joint Infections (PJIs) and Other Implant-Related Infections. *J. Clin. Med.* **2019**, *8* (7), 933.

(83) Tande, A. J.; Patel, R. Prosthetic Joint Infection. *Clin. Microbiol. Rev.* **2014**, *27* (2), 302–345.

(84) Hischebeth, G. T. R.; Gravius, S.; Buhr, J. K.; Molitor, E.; Wimmer, M. D.; Hoerauf, A.; Bekeredjian-Ding, I.; Randau, T. M. Novel Diagnostics in Revision Arthroplasty: Implant Sonication and Multiplex Polymerase Chain Reaction. *J. Vis. Exp.* **2017**, *2017* (130), 55147.

(85) Evangelopoulos, D. S.; Stathopoulos, I. P.; Morassi, G. P.; Koufos, S.; Albarni, A.; Karampinas, P. K.; Stylianakis, A.; Kohl, S.; Pneumaticos, S.; Vlamis, J. Sonication: A Valuable Technique for Diagnosis and Treatment of Periprosthetic Joint Infections. *Sci. World J.* **2013**, *2013*.

(86) Fernández-Sampedro, M.; Fariñas-Alvarez, C.; Garces-Zarzalejo, C.; Alonso-Aguirre, M. A.; Salas-Venero, C.; Martínez-Martínez, L.; Fariñas, M. C. Accuracy of Different Diagnostic Tests for Early, Delayed and Late Prosthetic Joint Infection. *BMC Infect. Dis.* **2017**, *17* (1), 592.

(87) Penny, C.; Gruffaz, C.; Nadalig, T.; Cauchie, H.-M.; Vuilleumier, S.; Bringel, F. Tetrachloromethane-Degrading Bacterial Enrichment Cultures and Isolates from a Contaminated Aquifer. *Microorganisms* **2015**, *3* (3), 327–343.

(88) Wieme, A. D.; Spitaels, F.; Aerts, M.; De Bruyne, K.; Van Landschoot, A.; Vandamme, P. Effects of Growth Medium on Matrix-Assisted Laser Desorption-Ionization Time of Flight Mass Spectra: A Case Study of Acetic Acid Bacteria. *Appl. Environ. Microbiol.* **2014**, *80* (4), 1528–1538.

(89) El-Metwally, S.; Ouda, O. M.; Helmy, M. *Next Generation Sequencing Technologies and Challenges in Sequence Assembly*; SpringerBriefs in Systems Biology; Springer New York, 2014; Vol. 7.

(90) Arca-Suárez, J.; Galán-Sánchez, F.; Marin-Casanova, P.; Rodríguez-Iglesias, M. A. Direct Identification of Microorganisms from Thioglycolate Broth by MALDI-TOF MS. *PLoS One* **2017**, *12* (9), e0185229.

(91) Kamaruzzaman, N. F.; Tan, L. P.; Yazid, K. A. M.; Saeed, S. I.; Hamdan, R. H.; Choong, S. S.; Wong, W. K.; Chivu, A.; Gibson, A. J. Targeting the Bacterial Protective Armour; Challenges and Novel Strategies in the Treatment of Microbial Biofilm. *Materials (Basel).* **2018**, *11* (9), 1705.

(92) Almatroudi, A.; Gosbell, I. B.; Hu, H.; Jensen, S. O.; Espedido, B. A.; Tahir, S.; Glasbey, T. O.; Legge, P.; Whiteley, G.; Deva, A.; Vickery, K. Staphylococcus Aureus Dry-Surface Biofilms Are Not Killed by Sodium Hypochlorite: Implications for Infection Control. *J. Hosp. Infect.* **2016**, *93* (3), 263–270.

(93) Vickery, K. *Microbial Biofilms in Healthcare: Formation, Prevention and Treatment*; MDPI AG, 2020.

(94) Rigo, S.; Cai, C.; Gunkel-Grabole, G.; Maurizi, L.; Zhang, X.; Xu, J.; Palivan, C. G. Nanoscience-Based Strategies to Engineer Antimicrobial Surfaces. *Adv. Sci.* **2018**, *5* (5), 1700892.

(95) Siedenbiedel, F.; Tiller, J. C. Antimicrobial Polymers in Solution and on Surfaces: Overview and Functional Principles. *Polymers (Basel).* **2012**, *4* (1), 46–71.

(96) Donelli, G. Biofilm-Based Healthcare-Associated Infections: Volume II. *Adv. Exp. Med. Biol.* **2015**, *831*.

(97) Zander, Z. K.; Becker, M. L. Antimicrobial and Antifouling Strategies for Polymeric Medical Devices. *ACS Macro Lett.* **2018**, *7* (1), 16–25.

(98) Ahmed, W.; Zhai, Z.; Gao, C. Adaptive Antibacterial Biomaterial Surfaces and Their Applications. *Mater. Today Bio* **2019**, *2*, 100017.

(99) Xu, Q.; Li, X.; Jin, Y.; Sun, L.; Ding, X.; Liang, L.; Wang, L.; Nan, K.; Ji, J.; Chen, H.; Wang, B. Bacterial Self-Defense Antibiotics Release from Organic-Inorganic Hybrid Multilayer Films for Long-Term Anti-Adhesion and Biofilm Inhibition Properties. *Nanoscale* **2017**, *9* (48), 19245–19254.

(100) Ishak, M. I.; Liu, X.; Jenkins, J.; Nobbs, A. H.; Su, B. Protruding Nanostructured Surfaces for Antimicrobial and Osteogenic Titanium Implants. *Coatings* **2020**, *10* (8), 756.

(101) Mas-Moruno, C.; Espanol, M.; Montufar, E. B.; Mestres, G.; Aparicio, C.; Gil, F. J.; Ginebra, M. P. Bioactive Ceramic and Metallic Surfaces for Bone Engineering. In *Biomaterials Surface Science*; Wiley-VCH Verlag, 2013; pp 337–374.

(102) Mas-Moruno, C.; Su, B.; Dalby, M. J. Multifunctional Coatings and Nanotopographies: Toward Cell Instructive and Antibacterial Implants. *Adv. Healthc. Mater.* **2019**, *8* (1), 1801103.

(103) Franci, G.; Falanga, A.; Galdiero, S.; Palomba, L.; Rai, M.; Morelli, G.; Galdiero, M. Silver Nanoparticles as Potential Antibacterial Agents. *Molecules* **2015**, *20* (5), 8856–8874.

(104) Dakal, T. C.; Kumar, A.; Majumdar, R. S.; Yadav, V. Mechanistic Basis of Antimicrobial Actions of Silver Nanoparticles. *Front. Microbiol.* **2016**, *7* (NOV), 1831.

(105) Bai, R.; Peng, L.; Sun, Q.; Zhang, Y.; Zhang, L.; Wei, Y.; Han, B. Metallic Antibacterial Surface Treatments of Dental and Orthopedic Materials. *Materials (Basel).* **2020**, *13* (20), 4594.

(106) Saidin, S.; Jumat, M. A.; Mohd Amin, N. A. A.; Saleh Al-Hammadi, A. S. Organic and Inorganic Antibacterial Approaches in Combating Bacterial Infection for Biomedical Application. *Mater. Sci. Eng. C* **2021**, *118*, 111382.

(107) Macomber, L.; Imlay, J. A. The Iron-Sulfur Clusters of Dehydratases Are Primary

Intracellular Targets of Copper Toxicity. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (20), 8344–8349.

(108) Ruparelia, J. P.; Chatterjee, A. K.; Duttagupta, S. P.; Mukherji, S. Strain Specificity in Antimicrobial Activity of Silver and Copper Nanoparticles. *Acta Biomater.* **2008**, *4* (3), 707–716.

(109) Ingle, A. P.; Duran, N.; Rai, M. Bioactivity, Mechanism of Action, and Cytotoxicity of Copper-Based Nanoparticles: A Review. *Appl. Microbiol. Biotechnol.* **2014**, *98* (3), 1001–1009.

(110) Schrand, A. M.; Rahman, M. F.; Hussain, S. M.; Schlager, J. J.; Smith, D. A.; Syed, A. F. Metal-based Nanoparticles and Their Toxicity Assessment. *Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology* **2010**, *2* (5), 544–568.

(111) Yoshida, Y.; Furuta, S.; Niki, E. Effects of Metal Chelating Agents on the Oxidation of Lipids Induced by Copper and Iron. *Biochim. Biophys. Acta (BBA)/Lipids Lipid Metab.* **1993**, *1210* (1), 81–88.

(112) Zare, M.; Namratha, K.; Thakur, M. S.; Yallappa, S.; Byrappa, K. Comprehensive Biological Assessment and Photocatalytic Activity of Surfactant Assisted Solvothermal Synthesis of ZnO Nanogranules. *Mater. Chem. Phys.* **2018**, *215*, 148–156.

(113) Talebian, N.; Amininezhad, S. M.; Doudi, M. Controllable Synthesis of ZnO Nanoparticles and Their Morphology-Dependent Antibacterial and Optical Properties. *J. Photochem. Photobiol. B Biol.* **2013**, *120*, 66–73.

(114) Heinlaan, M.; Ivask, A.; Blinova, I.; Dubourguier, H. C.; Kahru, A. Toxicity of Nanosized and Bulk ZnO, CuO and TiO2 to Bacteria Vibrio Fischeri and Crustaceans Daphnia Magna and Thamnocephalus Platyurus. *Chemosphere* **2008**, *71* (7), 1308–1316.

(115) Raghupathi, K. R.; Koodali, R. T.; Manna, A. C. Size-Dependent Bacterial Growth Inhibition and Mechanism of Antibacterial Activity of Zinc Oxide Nanoparticles. *Langmuir* **2011**, *27* (7), 4020–4028.

(116) Aydin Sevinç, B.; Hanley, L. Antibacterial Activity of Dental Composites Containing Zinc Oxide Nanoparticles. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2010**, *9999B* (1), NA-NA.

(117) Su, Y.; Cockerill, I.; Wang, Y.; Qin, Y. X.; Chang, L.; Zheng, Y.; Zhu, D. Zinc-Based Biomaterials for Regeneration and Therapy. *Trends Biotechnol.* **2019**, *37* (4), 428–441.

(118) Zare, M.; Namratha, K.; Byrappa, K. Green Synthesis and Characterization of ZnO- Ag Nanocomposite by Thymus Vulgaris. *Int. J. Sci. Res. Sci. Technol.* **2018**, *4* (5), 1636–1640.

(119) Zare, M.; Namratha, K.; Ilyas, S.; Hezam, A.; Mathur, S.; Byrappa, K. Smart Fortified PHBV-CS Biopolymer with ZnO–Ag Nanocomposites for Enhanced Shelf Life of Food Packaging. *ACS Appl. Mater. Interfaces* **2019**, *11* (51), 48309–48320.

(120) Uma Suganya, K. S.; Govindaraju, K.; Ganesh Kumar, V.; Stalin Dhas, T.; Karthick, V.; Singaravelu, G.; Elanchezhiyan, M. Blue Green Alga Mediated Synthesis of Gold Nanoparticles and Its Antibacterial Efficacy against Gram Positive Organisms. *Mater. Sci. Eng. C* **2015**, *47*, 351–356.

(121) Badwaik, V. D.; Vangala, L. M.; Pender, D. S.; Willis, C. B.; Aguilar, Z. P.; Gonzalez, M. S.; Paripelly, R.; Dakshinamurthy, R. Size-Dependent Antimicrobial Properties of Sugarencapsulated Gold Nanoparticles Synthesized by a Green Method. *Nanoscale Res. Lett.* **2012**, *7* (1), 623.

(122) Zhao, Y.; Tian, Y.; Cui, Y.; Liu, W.; Ma, W.; Jiang, X. Small Molecule-Capped Gold Nanoparticles as Potent Antibacterial Agents That Target Gram-Negative Bacteria. *J. Am. Chem. Soc.* **2010**, *132* (35), 12349–12356.

(123) Cui, Y.; Zhao, Y.; Tian, Y.; Zhang, W.; Lü, X.; Jiang, X. The Molecular Mechanism of Action of Bactericidal Gold Nanoparticles on Escherichia Coli. *Biomaterials* **2012**, *33* (7), 2327–2333.

(124) Cheung, H. Y.; Wong, M. M. K.; Cheung, S. H.; Liang, L. Y.; Lam, Y. W.; Chiu, S. K. Differential Actions of Chlorhexidine on the Cell Wall of Bacillus Subtilis and Escherichia Coli. *PLoS One* **2012**, *7* (5), 36659.

(125) Van Oosten, B. J.; Komljenovic, I.; Marquardt, D.; Sternin, E.; Harroun, T. Small Molecule Interaction with Lipid Bilayers: A Molecular Dynamics Study of Chlorhexidine. *Biophys. J.* **2013**, *104* (2), 242a.

(126) Greenhalgh, R.; Dempsey-Hibbert, N. C.; Whitehead, K. A. Antimicrobial Strategies to Reduce Polymer Biomaterial Infections and Their Economic Implications and Considerations. *Int. Biodeterior. Biodegrad.* **2019**, *136*, 1–14.

(127) Joshi, A. S.; Thompson, M. N.; Fei, N.; Ttemann, M. H.; Greenberg, M. L. Cardiolipin and Mitochondrial Phosphatidylethanolamine Have Overlapping Functions in Mitochondrial Fusion in Saccharomyces Cerevisiae. *J. Biol. Chem.* **2012**, *287* (21), 17589–17597.

(128) Moser, R.; Aktas, M.; Fritz, C.; Narberhaus, F. Discovery of a Bifunctional Cardiolipin/Phosphatidylethanolamine Synthase in Bacteria. *Mol. Microbiol.* **2014**, *92* (5), 959–972.

(129) Lopes, S. C.; Ivanova, G.; de Castro, B.; Gameiro, P. Cardiolipin and Phosphatidylethanolamine Role in Dibucaine Interaction with the Mitochondrial Membrane. *Biochim. Biophys. Acta - Biomembr.* **2019**, *1861* (6), 1152–1161.

(130) Sivaraman, K.; Chopra, A.; Narayana, A.; Radhakrishnan, R. A. A Five-Step Risk Management Process for Geriatric Dental Practice during SARS-CoV-2 Pandemic. *Gerodontology* **2020**, *38* (1), 17–2.

(131) Eggers, M. Infectious Disease Management and Control with Povidone Iodine. *Infect. Dis. Ther.* **2019**, *8* (4), 581–593.

(132) Anderson, D. E.; Sivalingam, V.; Kang, A. E. Z.; Ananthanarayanan, A.; Arumugam, H.; Jenkins, T. M.; Hadjiat, Y.; Eggers, M. Povidone-Iodine Demonstrates Rapid In Vitro Virucidal Activity Against SARS-CoV-2, The Virus Causing COVID-19 Disease. *Infect. Dis. Ther.* **2020**, *9* (3), 669–675.

(133) Pereira, B. M. P.; Tagkopoulos, I. Benzalkonium Chlorides: Uses, Regulatory Status, and Microbial Resistance. *Applied and Environmental Microbiology*. American Society for Microbiology 2019.

(134) Ioannou, C. J.; Hanlon, G. W.; Denyer, S. P. Action of Disinfectant Quaternary

Ammonium Compounds against Staphylococcus Aureus. *Antimicrob. Agents Chemother.* **2007**, *51* (1), 296–306.

(135) Jennings, M. C.; Minbiole, K. P. C.; Wuest, W. M. Quaternary Ammonium Compounds: An Antimicrobial Mainstay and Platform for Innovation to Address Bacterial Resistance. *ACS Infectious Diseases*. American Chemical Society January 8, 2016, pp 288–303.

(136) Kim, M.; Weigand, M. R.; Oh, S.; Hatt, J. K.; Krishnan, R.; Tezel, U.; Pavlostathis, S. G.; Konstantinidis, K. T. Widely Used Benzalkonium Chloride Disinfectants Can Promote Antibiotic Resistance. *Appl. Environ. Microbiol.* **2018**, *84* (17), e01201-18.

(137) Parikh, S. L.; Xiao, G.; Tonge, P. J. Inhibition of InhA, the Enoyl Reductase from Mycobacterium Tuberculosis, by Triclosan and Isoniazid. *Biochemistry* **2000**, *39* (26), 7645–7650.

(138) Wright, H. T.; Reynolds, K. A. Antibacterial Targets in Fatty Acid Biosynthesis. *Curr. Opin. Microbiol.* **2007**, *10* (5), 447–453.

(139) Fraise, A. P.; Maillard, J. Y.; Sattar, S. A. *Principles and Practice of Disinfection, Preservation and Sterilization*; Fraise, A. P., Maillard, J.-Y., Sattar, S. A., Eds.; Wiley-Blackwell: Oxford, UK, 2013.

(140) Kavanagh, K. *Fungi: Biology and Applications, 2nd Edition | Wiley*; A John Wiley & Sons, Ltd., 2011.

(141) K. Mazu, T.; A. Bricker, B.; Flores-Rozas, H.; Y. Ablordeppey, S. The Mechanistic Targets of Antifungal Agents: An Overview. *Mini-Reviews Med. Chem.* **2016**, *16* (7), 555–578.

(142) van Vugt, T. A. G.; Arts, J. J.; Geurts, J. A. P. Antibiotic-Loaded Polymethylmethacrylate Beads and Spacers in Treatment of Orthopedic Infections and the Role of Biofilm Formation. *Front. Microbiol.* **2019**, *10*.

(143) Gogia, J.; Meehan, J.; Di Cesare, P.; Jamali, A. Local Antibiotic Therapy in Osteomyelitis. *Semin. Plast. Surg.* **2009**, *23* (02), 100–107.

(144) Wheeless, C. R. *Wheeless' Textbook of Orthopaedics*; 2016.

(145) Stavrakis, A. I.; Niska, J. A.; Shahbazian, J. H.; Loftin, A. H.; Ramos, R. I.; Billi, F.; Francis, K. P.; Otto, M.; Bernthal, N. M.; Uslan, D. Z.; Miller, L. S. Combination Prophylactic Therapy with Rifampin Increases Efficacy against an Experimental Staphylococcus Epidermidis Subcutaneous Implant-Related Infection. *Antimicrob. Agents Chemother.* **2014**, *58* (4), 2377–2386.

(146) Donlan, R. M. Biofilms on Central Venous Catheters: Is Eradication Possible? *Curr. Top. Microbiol. Immunol.* **2008**, *322*, 133–161.

(147) Ma, Z.; Lynch, A. S. Development of a Dual-Acting Antibacterial Agent (TNP-2092) for the Treatment of Persistent Bacterial Infections. *J. Med. Chem.* **2016**, *59* (14), 6645–6657.

(148) Chang, T. M. S. Platelet Surface Interaction: Effect of Albumin Coating or Heparin Complexing on Thrombogenic Surfaces. *Can. J. Physiol. Pharmacol.* **1974**, *52* (2), 275–285.

(149) Katsikogianni, M.; Missirlis, Y. F.; Harris, L.; Douglas, J. Concise Review of Mechanisms of Bacterial Adhesion to Biomaterials and of Techniques Used in Estimating

Bacteria-Material Interactions. *Eur. Cells Mater.* **2004**, *8*, 37–57.

(150) Ngo, B. K. D.; Grunlan, M. A. Protein Resistant Polymeric Biomaterials. *ACS Macro Lett.* **2017**, *6* (9), 992–1000.

(151) Achinas, S.; Charalampogiannis, N.; Euverink, G. J. W. A Brief Recap of Microbial Adhesion and Biofilms. *Appl. Sci.* **2019**, *9* (14), 2801.

(152) Kolewe, K. W.; Zhu, J.; Mako, N. R.; Nonnenmann, S. S.; Schiffman, J. D. Bacterial Adhesion Is Affected by the Thickness and Stiffness of Poly(Ethylene Glycol) Hydrogels. *ACS Appl. Mater. Interfaces* **2018**, *10* (3), 2275–2281.

(153) Ozcelik, B.; Ho, K. K. K.; Glattauer, V.; Willcox, M.; Kumar, N.; Thissen, H. Poly(Ethylene Glycol)-Based Coatings Combining Low-Biofouling and Quorum-Sensing Inhibiting Properties to Reduce Bacterial Colonization. *ACS Biomater. Sci. Eng.* **2017**, *3* (1), 78–87.

(154) Roosjen, A.; Kaper, H. J.; van der Mei, H. C.; Norde, W.; Busscher, H. J. Inhibition of Adhesion of Yeasts and Bacteria by Poly(Ethylene Oxide)-Brushes on Glass in a Parallel Plate Flow Chamber. *Microbiology* **2003**, *149* (11), 3239–3246.

(155) Kingshott, P.; Wei, J.; Bagge-Ravn, D.; Gadegaard, N.; Gram, L. Covalent Attachment of Poly(Ethylene Glycol) to Surfaces, Critical for Reducing Bacterial Adhesion. *Langmuir* **2003**, *19* (17), 6912–6921.

(156) Wnorowska, U.; Fiedoruk, K.; Piktel, E.; Prasad, S. V.; Sulik, M.; Janion, M.; Daniluk, T.; Savage, P. B.; Bucki, R. Nanoantibiotics Containing Membrane-Active Human Cathelicidin LL-37 or Synthetic Ceragenins Attached to the Surface of Magnetic Nanoparticles as Novel and Innovative Therapeutic Tools: Current Status and Potential Future Applications. *J. Nanobiotechnology* **2020**, *18* (1), 1–18.

(157) Singha, P.; Locklin, J.; Handa, H. A Review of the Recent Advances in Antimicrobial Coatings for Urinary Catheters. *Acta Biomater.* **2017**, *50*, 20–40.

(158) Pushpanathan, M.; Gunasekaran, P.; Rajendhran, J. Antimicrobial Peptides: Versatile Biological Properties. *Int. J. Pept.* **2013**, *2013*.

(159) Omardien, S.; Brul, S.; Zaat, S. A. J. Antimicrobial Activity of Cationic Antimicrobial Peptides against Gram-Positives: Current Progress Made in Understanding the Mode of Action and the Response of Bacteria. *Front. Cell Dev. Biol.* **2016**, *4* (OCT), 111.

(160) Malanovic, N.; Lohner, K. Antimicrobial Peptides Targeting Gram-Positive Bacteria. *Pharmaceuticals* **2016**, *9* (3), 59.

(161) Yasir, M.; Willcox, M.; Dutta, D. Action of Antimicrobial Peptides against Bacterial Biofilms. *Materials (Basel).* **2018**, *11* (12), 2468.

(162) Kazemi Ashtiani, M.; Zandi, M.; Shokrollahi, P.; Ehsani, M.; Baharvand, H. Chitosan Surface Modified Hydrogel as a Therapeutic Contact Lens. *Polym. Adv. Technol.* **2020**, *31* (4), 741–748.

(163) Su, X.; Chen, L.; Han, S.; Niu, G.; Ren, J.; Ke, C. Preparation and Characterization of a Novel Triple Composite Scaffold Containing Silk Fiborin, Chitosan, and Alginate for 3D Culture of Colonic Carcinoma Cells In Vitro. *Med. Sci. Monit.* **2020**, *26*, e922935.

(164) Liu, R.; Miller, P. A.; Vakulenko, S. B.; Stewart, N. K.; Boggess, W. C.; Miller, M. J. A

Synthetic Dual Drug Sideromycin Induces Gram-Negative Bacteria to Commit Suicide with a Gram-Positive Antibiotic. *J. Med. Chem.* **2018**, *61* (9), 3845–3854.

(165) Shariatinia, Z. Pharmaceutical Applications of Chitosan. *Adv. Colloid Interface Sci.* **2019**, *263*, 131–194.

(166) Costa, E.; Silva, S.; Tavaria, F.; Pintado, M. Antimicrobial and Antibiofilm Activity of Chitosan on the Oral Pathogen Candida Albicans. *Pathogens* **2014**, *3* (4), 908–919.

(167) Sambanthamoorthy, K.; Feng, X.; Patel, R.; Patel, S.; Paranavitana, C. Antimicrobial and Antibiofilm Potential of Biosurfactants Isolated from Lactobacilli against Multi-Drug-Resistant Pathogens. *BMC Microbiol.* **2014**, *14* (1), 1–9.

(168) Kaur, D. M.; Patil, R. N.; Saima, A. Candida Albicans Biofilm Inhibition. *J Pure Appl Microbiol* **2020**, *14* (2), 1337–1343.

(169) Shokouhfard, M.; Kermanshahi, R. K.; Shahandashti, R. V.; Feizabadi, M. M.; Teimourian, S. The Inhibitory Effect of a Lactobacillus Acidophilus Derived Biosurfactant on Biofilm Producer Serratia Marcescens. *Iran. J. Basic Med. Sci.* **2015**, *18* (10), 1001–1007.

(170) Ceresa, C.; Tessarolo, F.; Caola, I.; Nollo, G.; Cavallo, M.; Rinaldi, M.; Fracchia, L. Inhibition of Candida Albicans Adhesion on Medical-Grade Silicone by a Lactobacillus - Derived Biosurfactant. *J. Appl. Microbiol.* **2015**, *118* (5), 1116–1125.

(171) Zaruta, D. A.; Qiu, B.; Liu, A. Y.; Ricciardi, B. F. Indications and Guidelines for Debridement and Implant Retention for Periprosthetic Hip and Knee Infection. *Curr. Rev. Musculoskelet. Med.* **2018**, *11* (3), 347–356.

(172) Iza, K.; Foruria, X.; Moreta, J.; Uriarte, I.; Loroño, A.; Aguirre, U.; De Los Mozos, J. L. M. DAIR (Debridement, Antibiotics and Implant Retention) Less Effective in Hematogenous Total Knee Arthroplasty Infections. *J. Orthop. Surg. Res.* **2019**, *14* (1), 1–6.

(173) Ferry, T.; Batailler, C.; Petitjean, C.; Chateau, J.; Fevre, C.; Forestier, E.; Brosset, S.; Leboucher, G.; Kolenda, C.; Laurent, F.; Lustig, S. The Potential Innovative Use of Bacteriophages Within the DAC® Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring "Debridement Antibiotics and Implant Retention" and Soft Tissue Coverage as Salvage Therapy. *Front. Med.* **2020**, *7*, 342.

(174) Kini, S. G.; Gabr, A.; Das, R.; Sukeik, M.; Haddad, F. S. Two-Stage Revision for Periprosthetic Hip and Knee Joint Infections. *Open Orthop. J.* **2017**, *10* (Suppl-2, M2), 579–588.

(175) Fagotti, L.; Tatka, J.; Salles, M. J. C.; Queiroz, M. C. Risk Factors and Treatment Options for Failure of a Two-Stage Exchange. *Curr. Rev. Musculoskelet. Med.* **2018**, *11* (3), 420–427.

(176) Lee, Y. S.; Chen, A. F. Two-Stage Reimplantation in Infected Total Knee Arthroplasty. *Knee Surg. Relat. Res.* **2018**, *30* (2), 107–114.

(177) Yaghmour, K.; Chisari, E.; Khan, W. Single-Stage Revision Surgery in Infected Total Knee Arthroplasty: A PRISMA Systematic Review. *J. Clin. Med.* **2019**, *8* (2), 174.

(178) Sharma, D.; Misba, L.; Khan, A. U. Antibiotics versus Biofilm: An Emerging

Battleground in Microbial Communities. *Antimicrob. Resist. Infect. Control* **2019**, *8*, 76.

(179) Lebeaux, D.; Ghigo, J.-M.; Beloin, C. Biofilm-Related Infections: Bridging the Gap between Clinical Management and Fundamental Aspects of Recalcitrance toward Antibiotics. *Microbiol. Mol. Biol. Rev.* **2014**, *78* (3), 510–543.

(180) Vorkapic, D.; Pressler, K.; Schild, S. Multifaceted Roles of Extracellular DNA in Bacterial Physiology. *Curr. Genet.* **2016**, *62* (1), 71–79.

(181) Zare, M.; Sillanpää, M.; Ramakrishna, S. Essential Role of Quantum Science and Nanoscience in Antiviral Strategies for COVID-19. *Mater. Adv.* **2021**, *2*, 2188–2199.

(182) Farr, R.; Choi, D. S.; Lee, S.-W. Phage-Based Nanomaterials for Biomedical Applications. *Acta Biomater.* **2014**, *10* (4), 1741–1750.

(183) Hosseinidoust, Z.; Olsson, A. L. J.; Tufenkji, N. Going Viral: Designing Bioactive Surfaces with Bacteriophage. *Colloids Surfaces B Biointerfaces* **2014**, *124*, 2–16.

(184) Hyman, P.; Denyes, J. Bacteriophages in Nanotechnology: History and Future. In *Bacteriophages*; Springer International Publishing, 2021; pp 657–687.

(185) Paczesny, J.; Bielec, K. Application of Bacteriophages in Nanotechnology. *Nanomaterials* **2020**, *10* (10), 1944.

(186) Curtin, J. J.; Donlan, R. M. Using Bacteriophages to Reduce Formation of Catheter-Associated Biofilms by Staphylococcus Epidermidis. *Antimicrob. Agents Chemother.* **2006**, *50* (4), 1268–1275.

(187) Tang, H. J.; Lin, H. L.; Lin, Y. H.; Leung, P. O.; Chuang, Y. C.; Lai, C. C. The Impact of Central Line Insertion Bundle on Central Line-Associated Bloodstream Infection. *BMC Infect. Dis.* **2014**, *14* (1), 356.

(188) Safdar, N.; O'Horo, J. C.; Ghufran, A.; Bearden, A.; Didier, M. E.; Chateau, D.; Maki, D. G. Chlorhexidine-Impregnated Dressing for Prevention of Catheter-Related Bloodstream Infection: A Meta-Analysis. *Crit. Care Med.* **2014**, *42* (7), 1703–1713.

(189) Baddour, L. M.; Epstein, A. E.; Erickson, C. C.; Knight, B. P.; Levison, M. E.; Lockhart, P. B.; Masoudi, F. A.; Okum, E. J.; Wilson, W. R.; Beerman, L. B.; Bolger, A. F.; Estes, N. A. M.; Gewitz, M.; Newburger, J. W.; Schron, E. B.; Taubert, K. A. Update on Cardiovascular Implantable Electronic Device Infections and Their Management: A Scientific Statement from the American Heart Association. *Circulation* **2010**, *121* (3), 458–477.

(190) Flodgren, G.; Conterno, L. O.; Mayhew, A.; Omar, O.; Pereira, C. R.; Shepperd, S. Interventions to Improve Professional Adherence to Guidelines for Prevention of Device-Related Infections. *Cochrane Database Syst. Rev.* **2013**, *28* (3), CD006559.

(191) Tan, J.; Shah, S.; Thomas, A.; Ou-Yang, H. D.; Liu, Y. The Influence of Size, Shape and Vessel Geometry on Nanoparticle Distribution. *Microfluid. Nanofluidics* **2013**, *14* (1–2), 77–87.

(192) Schoephoerster, R. T.; Oynes, F.; Nunez, G.; Kapadvanjwala, M.; Dewanjee, M. K. Effects of Local Geometry and Fluid Dynamics on Regional Platelet Deposition on Artificial Surfaces. *Arterioscler. Thromb. Vasc. Biol.* **1993**, *13* (12), 1806–1813.

(193) Bluestein, D.; Einav, S.; Slepian, M. J. Device Thrombogenicity Emulation: A Novel

Methodology for Optimizing the Thromboresistance of Cardiovascular Devices. *J. Biomech.* **2013**, *46* (2), 338–344.

(194) Clark, T. W. I.; Isu, G.; Gallo, D.; Verdonck, P.; Morbiducci, U. Comparison of Symmetric Hemodialysis Catheters Using Computational Fluid Dynamics. *J. Vasc. Interv. Radiol.* **2015**, *26* (2), 252-259.e2.

(195) Lai, N. M.; Chaiyakunapruk, N.; Lai, N. A.; O'Riordan, E.; Pau, W. S. C.; Saint, S. Catheter Impregnation, Coating or Bonding for Reducing Central Venous Catheter-Related Infections in Adults. *Cochrane Database Syst. Rev.* **2016**, *3* (3), CD007878.

(196) Hochbaum, A. I.; Aizenberg, J. Bacteria Pattern Spontaneously on Periodic Nanostructure Arrays. *Nano Lett.* **2010**, *10* (9), 3717–3721.

(197) Decuzzi, P.; Ferrari, M. Modulating Cellular Adhesion through Nanotopography. *Biomaterials* **2010**, *31* (1), 173–179.