Antibacterial Designs for Implantable Medical Devices

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The uses of implantable medical devices are safer and more common since sterilization methods and techniques were established a century ago; however, device-associated infections (DAIs) are still frequent and becoming a leading complication as the number of medical device implantations keeps increasing.

Keywords: Biomaterials ; Antibacterial surface ; Implantable medical devices ; Titanium ; Biocompatibility

1. Introduction

It was estimated that over 500,000 types of medical devices, such as dental implants, vascular graft/endograft, orthopedic prosthetics, catheters, etc., are currently marketing globally for medical applications [1]. Every year, there are about 10,000,000 dental implants and more than 1,000,000 cardiovascular electronic devices inserted around the world [2][3]. It has been estimated that 100 million urinary catheters are sold worldwide each year [4]. As the population of the aged increases, procedures for implantable medical devices are expected to increase rapidly in the coming years. In the United States of America (USA), the primary total knee arthroplasty (TKA) is going to grow by 85%, to 1.26 million procedures by 2030 [5]. In Germany, by 2040, the total number of TKA is expected to increase by 45% to over 244,000 procedures; and the incidence rate of total hip arthroplasty (THA) is projected to increase to 437 per 100,000 inhabitants [6]. In the United Kingdom, the volume of hip and knee joint replacement is expected to increase by almost 40% by 2060 [7]. Bacterial infections are one of the most frequent and severe complications associated with the clinical application of implantable medical devices [1]. It was reported that device-associated infections (DAIs), including ventilator-associated pneumonia, catheter-associated urinary tract infection, and central-catheter-associated bloodstream infection), accounted for approximately 26% of all healthcare-associated infections (HAIs) in the USA [8]. The annual number of HAIs in European Union countries is about 3.2 million, including 37,000 registered mortalities [9]. The financial burden for the treatment of a DAI is also extraordinarily high. For instance, the average revision costs in the USA for infected hip and knee arthroplasty were approximately USD 80 and 60 thousand, respectively [10]. Additionally, by 2030, the estimated combined annual hospital costs related to arthroplasty infection will rise to USD 1.85 billion in the USA alone [11]. This urges the world to develop instructive prevention and treatment strategies for DAIs.

Accordingly, fundamental research on the development of various antibacterial surfaces has dramatically increased in recent years. Screening for "*antibacterial surface*" or "*antibacterial coating*" in the topic of the articles included in the Web of Science (*www.webofscience.com*; accessed on 14 February 2022) can hit more than 50,000 records between the years 1996 and 2021. Around 80% of these records were published during the last decade (between 2012 and 2021), and over 67% of them were published during the last five years (between 2017 and 2021), identifying a boom in developing antibacterial surfaces or coatings. Developing antibacterial surfaces for implantable medical devices also is currently a hot direction among the Chinese communities focusing on biomaterials science and engineering. Typical designs published in the first half of 2022 include copper-bearing titanium [12], surface charge and wettability control in lysozyme [13], light-activatable carbon monoxide gas generation by triiron dodecacarbonyl loaded polydopamine [14], clickable peptide engineered surface [15], calcium-doped titanium targeting blood protein adsorption [16], puncture and ROS (reactive oxygen species) release by nanorod zinc oxide patterns [17], light-stimulated ROS generation by rare-earth elements-doped titanium dioxide coating [18], on-demand antibiotics release by responsive polymers [19][20], and bacteriophage-modified alginate hydrogels [21]. This trend demonstrates that the academic community has already realized the urgency of solving the DAI problem, whereas only a limited number of these innovations have entered clinical applications or clinical studies around the world. A very small number of registered records concerning antibacterial surfaces were found in *ClinicalTrials.gov* (accessed on 22 May 2022) by searching for "*device infection*" in the "*Condition or disease*" field. As shown in **Table 1**, silver in metallic or ionic forms is the most popular active ingredient in developing antibacterial medical devices. Currently, a handful of antibacterial surfaces have been branded for clinical uses, which are commonly silver-based and normally custom-made (available on request). These include *Acticoat* using magnetron sputtering synthesized nanosilver coatings for wound care [22], *MUTARS* prosthesis reducing infections by electroplating a metallic-silver surface,

METS prosthesis acting against pathogenic bacteria by absorption of ionic silver to anodized titanium implants [23], *PorAg* prosthesis taking advantage of a controlled electrochemical reaction (do not directly release silver ions) in a titanium-silver alloy for disinfection [23], and *PROtect* nails administrating gentamicin for prevention of infections in complex open fractures [24]. These commercial promotions have set examples for the development of antibacterial surfaces for implantable medical devices; however, it is still a challenge to improve the quality and efficiency of translational research over those "*antibacterial surface*" or "*antibacterial coating*" reports.

Table 1. Antibacterial surface registered for clinical studies *.

Active Ingredients	Devices	Phase	Locations	First Posted
Silver coating	Intravenous catheters	Not applicable	United States	25 August 2009
Antibiotics (minocycline and rifampin)	Antibacterial envelope for a cardiac implantable electronic device	Not applicable	United States	7 January 2010
Silver-based coating	Urinary catheter	Not applicable	United States	10 September 2012
Ionic silver	Wound dressings for a cardiac implantable electronic device	Phase 4	United States	24 May 2016
Silver-doped hydroxyapatite coating	Orthopedic implants (hip joint prostheses, intramedullary nails, and external fixator implants)	Not applicable	Turkey	17 November 2017
Gold-silver-palladium coating	Invasive devices (endotracheal tube, central venous catheter, and urinary catheter)	Phase 1, 2	Brazil	11 March 2019
Iodine	Barrier dressing for a cardiac implantable electronic device	Not applicable	Canada	19 October 2020
Antibiotic (gentamycin)	Platform wound device	Phase 4	United States	15 February 2021

* Data were obtained by searching for "*device infection*" in the "*Condition or disease*" field of the registered clinical studies conducted around the world on *ClinicalTrials.gov* (plus manual exclusion, as of 31 March 2022).

2. Clinical Features of Device-Associated Infections

2.1. Site-Specific Incidence

Infection is a common and frequent complication associated with all types of biomedical materials, despite the infection rate varying greatly among different intended uses of various implantable devices (**Table 2**) [25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61]. Orthopedic implants, such as the ankle, hip, knee, elbow, shoulder, and finger joint prosthetics, are made of metals (titanium alloys, stainless steel, cobalt-chromium alloy, etc.) and are expected to serve long periods (>10 years) in patients' bodies. Infections of these devices are extremely troublesome [1]. Ankle arthroplasty has higher infection rates (2.4–8.9%) than hip (0.4–2.4%) and knee (1–2%) arthroplasty, although they are normally made of the same materials (**Table 2**). This is remarkably related to wound dehiscence (or prolonged drainage) developed due to the frail soft tissue surrounding ankles and increased chance of delayed wound healing following ankle arthroplasty [26][62]. The infection situation will be even more serious in revision cases. For example, the incidence of infection for primary hip and knee arthroplasty is around 2% (**Table 2**), yet this will be possibly as high as 12% and 22% for revision hip and knee arthroplasty, respectively [63]. Moreover, the number of infection cases is expected to increase progressively because the number of arthroplasty surgeries is going to grow in the coming years. In Taiwan, China, for instance, a total of 728 hip and knee infection cases were recorded in 2013 and this number was expected to increase markedly to over 3500 by 2035 [10]. Not only these metallic implants are connected to bacterial infection, but also polymer devices are susceptible to this complication (**Table 2**). Examples include breast implants, vascular graft/endograft, cardiovascular electronic devices, and cochlear implants, which are made of silicone, polytetrafluoroethylene, plastics, or Teflon, and have infection incidence high up to 10.2% [32], 6% [33], 7% [37], and 8% [40], respectively. Additionally, the DAIs may occur due to the device design. As in brain stimulation implants, the battery of the pulse generator should be replaced typically every 2 years, and such multiple replacements increase the risk of DAIs [46]. Furthermore, the incidence of infection is highly determined by the site a device is placed in. As shown in **Table 2**, the infection rates in urinary catheters (up to 13.7 cases per 1000 catheter-days), cerebrospinal fluid shunts (27%), internal fixation devices (32%), and dental implants (47%) are high. This is because these devices are highly challenged by bacterial adhesion and biofilm formation during their insertion and the subsequent service period. For example, urinary

catheters provide routes for the entry of pathogenic bacteria, increasing the risk of acquiring infections [51]. Investigations of the bacterial sources in infected shunts also demonstrate that a majority of harmful microbes gained entry from the skin of the patients themselves [64]. The risk of complications in fixation of fractures is highly in connection to the low blood supply and elder people are susceptible to infection [59]. Additionally, there are more than 500 bacterial species associated with commensals or pathogens within the oral cavity [65]. This situation makes the prevention of infections in dental implants extremely complicated. The reported incidence rates for dental implants serving of over 3 and 5 years are 9.25% and 9.6%, respectively, and this rate for implants with service periods of over 10 years is up to 26% [61]. More importantly, the prevalence of the pathogenic strains is also associated with specific anatomical locations. Although *Staphylococcus* spp. is the most prevalent microbe associated with all types of bacterial infections, other pathogens can be involved in specific sites. Gram-negative microbes are involved in 10–40%, 20%, and 35–55% of vertebral, trauma/fracture, and foot/ankle-related infections [66]. Additionally, 15–30%, 20–30%, and 30–80% of polymicrobial infections occur in vertebral, trauma/fracture, and foot/ankle, respectively [66]. Different bacterial strains may have different metabolisms and pathogenic mechanisms that require specifically tailored treatments. This is especially critical to cure infections involving multiple pathogenic strains; as a result, developing an all-around antibacterial solution for all medical devices is hardly possible.

Table 2. Incidence of typical device-associated infections.

Device	Materials	Incidence	Reference
Ankle arthroplasty	**Metals (titanium alloys), Ceramic, Polyethylene**	**2.4–8.9%**	[25][26]
Hip arthroplasty	**Metals (titanium alloys, stainless steel), Ceramics (alumina, zirconia), Polymers (polyethylene, polyetheretherketone), Composites**	**0.4–2.4%**	[10][27][28]
Knee arthroplasty	**Metals (titanium alloys, cobalt-chromium alloy), Ceramics (zirconia, titanium nitride), Polymers (polyethylene,)**	**1–2%**	[10][29]
Breast implants	**Silicone**	**1–10.2%**	[30][31][32]
Vascular graft/endograft	**Polytetrafluoroethylene, Polyethylene Terephthalate, Nitinol**	**0.16–6%**	[33]
Cardiovascular electronic devices	**Plastic polymers, Titanium, Teflon, Gold, Copper**	**0.9–7%**	[34][35][36][37][38]
Cochlear implant	**Teflon, Platinum-iridium alloy, Silicone, Titanium, Ceramics**	**1–8%**	[39][40][41][42][43]
Brain stimulation implant	**Stainless steel, Platinum, Titanium oxide, Iridium oxide**	**2–10%**	[44][45][46]
Urinary catheters *	**Natural rubber, Polyisoprene, Polymer ethylene vinyl acetate, Polytetrafluoroethylene, Hydrogel**	**0.1–13.7 cases per 1000 catheter-days**	[47][48][49][50][51][52]
Cerebrospinal fluid shunts	**Silicone rubber**	**1.9–27%**	[53][54][55][56][57]
Internal fixation devices	**Stainless steel, Cobalt-chromium alloys, Titanium alloys**	**7–32%**	[58][59]
Dental implants	**Titanium, Ceramics (zirconia, alumina)**	**6–47%**	[60][61]

* The incidence of catheter-associated urinary tract infection is typically expressed as the number of infections per 1000 urinary catheter-days [52].

2.2. The Unpredictable Onset

Device-associated infections become even stickier because of those host-specific, transient, or resident factors (**Table 3**) [67][68][69][70][71][72][73][74][75][76][77][78][79]. The onset of DAI is not predictable, it can onset years after implantation (Cases 1 through 6 in **Table 3**). The soft tissue envelope around an implant likely degenerates with aging and can be disrupted by an occasional scratch, which may have promoted the infection of an alloplastic chin implant 45 years after placement [67]. Breast implants significantly risk bacterial contamination from hematogenous spread of distant antecedent infections. It was reported that the *Achromobacter xylosoxidans* (lives in wet soil) from a chronic footsore and *streptococcus viridans* (lives in the oral cavity) from recurrent periodontitis can cause infection of breast implants even 7 and 25 years after the implantation [68]. *Staphylococcus epidermidis* (*S. epidermidis*) can colonize various biomedical implants and escape from the immune clearance and antibiotic treatments, hence possibly causing symptom-free (such as pain,

redness, or fever) chronic infection lasting even for 30 years before being identified by clinical approaches [69]. *Cutibacterium acnes* (previously known as *propionibacterium acnes*), a common conjunctival inhabitant, are slow-growing, anaerobic Gram-positive rods, and can manifest several years or even decades before leading to late infections in orbital implants made of silicone or tantalum [70][71]. The sources of the pathogens of the DAIs can be host-specific (Cases 7 through 9 in **Table 3**). DAIs can be initiated by acute illness (e.g., diarrhea developed during a holiday journey [31]), penetration of contaminated water during participating in outdoor activities [45], or even when the patients play with their pets (bacterial contamination from zoonotic sources) [72]. Moreover, the occurrence of DAIs is commonly associated with a compromised immune system in the hosts (Cases 10 and 11 in **Table 3**). Methotrexate, a folate antagonist, can affect neutrophil chemotaxis and induce apoptosis of T cells and reactivation of opportunistic pathogens; hence chronic treatment of rheumatoid arthritis with this kind of drug significantly increases the risk of infections around the battery for brain stimulation [73]. *Nocardia nova* is a common environmental pathogen and rarely affects immunocompetent hosts; however, this species successfully colonized a tibia implant placed in an immunocompetent patient [74]. *Listeria monocytogenes*, a common organism associated with unpasteurized dairy products (e.g., deli meats and unpasteurized cheeses), can induce a periprosthetic joint infection in a patient with a history of diabetes mellitus, asthma, and psoriatic arthritis [75]. *Anaerobiospirillum succiniciproducens*, a common settler in the gastrointestinal tract of cats and dogs, can induce a prosthetic hip joint infection in an immunocompromised patient [76]. DAIs are normally initiated by bacterial seeding and as a result tissue integration will be impaired quickly; however, some cases failed to identify any organism by cultures [77][78] and tissue integration was intact after being infected [79]. These situations add difficulties to the prevention, diagnosis, and treatment of DAIs.

Table 3. Representative cases showing the latent period of DAIs.

Case	Devices	Latent Period (Post Insertion)	Pathogens	Causes	Reference
1	Alloplastic chin implant	45 years	/	After scratching herself (soft tissue degeneration due to aging)	[67]
2	Breast implant	Seven years	*Achromobacter xylosoxidans* (a pathogen that lives in wet soil)	Development of a chronic footsore (hematogenous spread from distant bacterial infection sites)	[68]
3	Breast implant	25 years	*Streptococcus viridans* (a pathogen that lives in the oral cavity)	After extensive dental treatment (hematogenous spread from distant bacterial infection sites)	[68]
4	Alloplastic implant	30 years	*Staphylococcus epidermidis*	Bacterial contamination years before identifying the infection (a symptom-free chronic infection; the pathogen escaped immune clearance and antibiotic treatments)	[69]
5	Orbital implant	30 years	*Cutibacterium acnes* (previously known as *Propionibacterium acnes*)	Bacterial contamination during the primary implantation (the pathogen can manifest for several decades)	[70]
6	Orbital implant	26 years (implant exposure 10 years before the presentation was documented)	*Propionibacterium acnes (renamed Cutibacterium acnes)*	Bacterial contamination during the primary implantation or implant exposure during scleral patch graft repair	[71]
7	Breast Implant	Five months	*Salmonella serogroup C*	Hematogenous seeding due to developing of diarrhea during a holiday travel	[31]
8	Generator for brain stimulation	Four months	Multispecies including the rare *Cupriavidus pauculus species* (an environmental Pathogen in "*water*")	Penetration of contaminated water during participating in outdoor activities	[45]
9	Breast implant	Seven months	*Pasteurella canis* (a pathogen normally lives in the oropharyngeal commensal flora of cats and dogs)	Bacterial contamination from a patient-owned cat	[72]

Case	Devices	Latent Period (Post Insertion)	Pathogens	Causes	Reference
10	Battery for brain stimulation	Two cases (Two years or 10 years)	*Staphylococcus aureus*	Chronic treatment of rheumatoid arthritis with methotrexate	[73]
11	Tibia Tenodesis Implant	Four and half months	*Nocardia nova* (a common environmental pathogen, rarely affects immunocompetent hosts)	Contamination of his tibial wound by the outside facility	[74]
12	Knee arthroplasty	4 months	*Listeria monocytogenes* (a facultative intracellular organism; commonly associated with deli meats and unpasteurized cheeses)	Consuming unpasteurized dairy products (an immunocompromised patient)	[75]
13	Hip arthroplasty	10 years	*Anaerobiospirillum succiniciproducens* (lives in the gastrointestinal tract of cats and dogs)	Breeding a dog (an immunocompromised patient)	[76]
14	Knee arthroplasty	Eight years	*Bartonella henselae* (a pathogen that induces acute infections but is hard to be diagnosed by culture)	A cat scratch	[77]
15	Cranioplasty implant	Two years and three months	No bacteria were cultured, but the infection was clinically evident	/	[78]
16	Shoulder prosthesis	Three years	*Staphylococcus* spp.	/	[79]

2.3. Diversity of Relevant Pathogens

Infections associated with medical devices with the same intended use (the same device category) but placed in different individuals are possibly connected with different bacterial strains. As shown in **Table 3**, the infection of breast implants can result from *achromobacter xylosoxidans* (Gram-negative rod) [68], *streptococcus viridans* [68], and *salmonella serogroup C* [31], or *Pasteurella canis* [72]. Polymicrobial infections become more prevalent in DAIs [66][80]. Even a single infection in a specific individual often has a polymicrobial composition [81]. Multispecies including the rare *Cupriavidus pauculus* species were isolated in an infection associated with the generator for brain stimulation [45]. Since the bacteria associated with an infection of a medical device may have diverse morphologies and arrangements, an effective antibacterial strategy must be capable of eliminating multiple pathogenic species. *Cocci* cells (spherical bacteria) range from 0.5 to 2.0 μm in diameter, rods are approximate 0.5–1.0 μm in width and 1–10 μm in length, and spiral bacteria are up to 20 μm in length and 0.1–1 μm in diameter [82]. Moreover, bacterial morphology varies with the growth environments (medium, surfaces, etc.) and growth phase (normally smallest in the logarithmic phase) [83][84]. These facts add additional difficulties to developing a competent antibacterial surface for implantable devices. On account of these features of DAIs, antibacterial surfaces only have a pore-size-based cell selectivity [85], or those peptide-loaded surfaces merely have specific actions to Gram-positive or Gram-negative strains [86] and are not likely adequate to prevent infection of implantable medical devices.

2.4. Prevalence of Antibiotic Resistance

The uses of internal implants in humans are safer and more common since sterilization methods and techniques were established at the end of the 19th century [87], and the commercialization of antibiotics especially penicillin in the first half of the 20th century [88]. Antibiotics have become an integral component of contemporary biomedical practice, producing a serious follow-up threat: antibiotic resistance in bacteria [89][90]. Clinical cases in orthopedic practice have shown that infections of antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are closely related to high morbidity and mortality [91]. Antibiotic resistance in bacteria even multidrug-resistant (MDR) bacteria is now a worldwide challenge [91]. Antibiotic-resistant infections were frequently reported all over the world, including in both developing and developed countries (**Table 4**) [92][93][94][95][96][97][98][99][100][101][102][103][104][105][106][107][108][109][110]. During an infection, *Staphylococcus aureus* (*S. aureus*) often forms biofilms on implantable devices, which dramatically increases the ability of the species to acquire resistance via horizontal plasmid transfer [111]. This is why *S. aureus* has high rates of resistance. As shown by the typical cases reported in recent years (**Table 4**), MRSA has become the most common strain causing infections of various implantable medical devices, including cardiac devices [93][95][99][103][106], orthopedic

prosthetics [96][97], cochlear implants [98], breast implants [100], laryngeal implants [101], and stent grafts [109]. In addition, there is an alarming increase in antibiotic resistance in other strains, such as *Acinetobacter baumannii* [92], *Mycobacterium chelonae* [94], *Enterobacter cloacae complex* [102], *S. epidermidis* [104][110], *Klebsiella pneumoniae* [105], *Staphylococcus haemolyticus* [107], and *Staphylococcal endophthalmitis* [108], are also involved in various resistant DAIs. Those resistant DAIs impacted patients have to experience prolonged hospital stays, bear high medical costs, and risk increased mortality (references in **Table 4**). Antibiotic recalcitrance is a worldwide threat that likely causes substantial global economic costs ranging from USD 21,832 per individual case to over USD 3 trillion in gross domestic product (GDP) loss by 2050 [112]. In the USA alone, at least 2 million infections and 23,000 deaths per year were caused by antibiotic-resistant bacteria, costing USD 55–70 billion [90]. Currently, antibiotic-loaded materials are important complements to modular medical practices for the prevention of recurrent infections in various medical devices, such as wound dressings, bone cement, bone plates, nails, or prostheses [24][113][114]. However, applications of these surfaces in "*uninfected tissues*" to prevent DAIs should be careful and in strict guidance, because the prolonged release of prophylactic antibiotics possibly contributes to arising resistant mutants [115]. Silver-based surfaces also have attractive efficacy in the prevention of DAIs [116], improper use of this material may also pose bacterial-resistant problems [117][118]. In addition, pathogenic bacteria have many defensive actions resistant to antimicrobial challenges [91][119][120]: (a) express polymer biofilms to protect themselves from antibiotic attacks; (b) remodel their outer surface to reduce antibiotic uptake; (c) synthesize precursors to modify the target of antimicrobials; (d) produce enzymes to detoxify dangerous drugs. Therefore, antibacterial surfaces, especially those release-killing ones, should be designed to bypass these actions of bacterial cells.

Table 4. Epidemiology of antibiotic-resistant DAIs.

Case	Resistant Pathogens	Implant	Latent Period	Reference
1	***Multidrug-resistant Acinetobacter baumannii***	**Hip arthroplasty**	**12–25 days**	[92]
2	***Methicillin-resistant Staphylococcus aureus (MRSA)***	**Cardiac pacemaker**	**Nine years**	[93]
3	***Clarithromycin-resistant Mycobacterium chelonae***	**Breast implant**	**Four days**	[94]
4	***MRSA***	**Transvenous lead**	**Four years**	[95]
5	***MRSA***	**Ankle fracture fixation**	**Eight weeks**	[96]
6	***MRSA***	**Cranial implant**	**Three months**	[97]
7	***MRSA***	**Cochlear implant**	**Five months**	[98]
8	***MRSA***	**Pacemaker**	**Two months**	[99]
9	***MRSA***	**Breast Implant**	**Two days**	[100]
10	***MRSA***	**Laryngeal implant**	**More than one year**	[101]
11	***Carbapenem-resistant Acinetobacter baumannii; Fluoroquinolone-resistant Enterobacter cloacae complex (AmpC overexpression)***	**Internal fixation for an open proximal tibial fracture**	**Two months**	[102]
12	***MRSA***	**Pacemaker**	**Two years**	[103]
13	***Multidrug-resistant Staphylococcus epidermidis***	**Plates and wire cerclages for periprosthetic fractures**	**Three months**	[104]
14	***Carbapenem-resistant Klebsiella pneumoniae***	**Lumbar instruments,**	**Seven days**	[105]
15	***MRSA***	**The ventricular lead of an implanted defibrillator**	**Eight weeks**	[106]
16	***Methicillin-resistant Staphylococcus haemolyticus***	**Hip joint**	**Two years**	[107]
17	***Ofloxacin-resistant staphylococcal endophthalmitis***	**Intravitreal ozurdex implant**	**Three days**	[108]
18	***MRSA***	**Stent graft**	**Three days**	[109]
19	***Methicillin-resistant Staphylococcus epidermidis***	**Spinal instrumentation**	**7–88 days**	[110]

3. Innovative Designs to Mitigate Device-Associated Infections

3.1. Prolonged Antibacterial Efficacy

As shown by **Table 3** and **Table 4**, the latent period of a DAI can be days after implant placement [92][94][105][108][109][110], years after the surgery [78][79][93][95], or even decades later [67][68]. This feature of DAIs lays the basis for the development of antibacterial surfaces with long active durations. As shown by the representative reports on the development of "*long-term*" antibacterial surfaces (**Table 5**) [121][122][123][124][125][126][127][128][129][130][131][132][133][134][135][136][137][138][139], various ingredients such as commercial antibiotics (tigecycline, vancomycin, amoxicillin, etc.) [121][132], metals or metal ions (silver, copper, or zinc) [124][125][129], and other drugs [127][128] were taken to equip implantable biomaterials (titanium, silicone, ceramics, etc.) with prolonged antibacterial efficacy, ranging from days [127][131][133] to months [122][134]. Extending the release period of the antimicrobials is currently a major pathway leading to "*long-term*" antibacterial surfaces. Calcium phosphate cement (CPC) has proved an effective carrier to retain vancomycin (effective for the treatment of MRSA) to local sites [140][141], ensuring the antibiotic has a 24-week release profile in vivo [122]. Proper antibiotic concentration is a key factor that determines the mechanical strength of vancomycin-impregnated CPC and influences the effective antibacterial period of the composite [140]. Electrochemical oxidation, namely micro-arc oxidation (also known as plasma electrolytic oxidation) and anodic oxidation, is a well-known class of approaches that can produce porous surface layers on implant materials and, in the meantime, load antibacterial agents on the material's surface. Shivaram et al. demonstrated that the silver loaded in an anodized titanium substrate had a release period of a minimum of 6 months [134]. The titanium substrates were fabricated with 25 vol% porosity by using a powder-based additive manufacturing technique [142]. Then electrochemical anodization was applied to the porous titanium in a hydrofluoric acid electrolyte to produce a surface layer of nanotube arrays with a thickness of 375 ± 35 nm and diameter of 105 nm ± 30 nm, which facilitated the loading of silver from a 0.1 M silver nitrate ($AgNO_3$) solution via direct current deposition [134]. After heating at 500 °C, tightly adhered silver particles with a coverage of 13.5% were detected on the nanotube-structured surface. The 27-week cumulative release profiles demonstrated that silver release was within 10 ppm (mg/mL), which ensured good early-stage osseointegration of the porous titanium implants, along with good antibacterial activities [134]. Micro-arc oxidation is another technique that can produce a porous titanium surface which may facilitate the control of antimicrobial release. Very recently, Tsutsumi et al. reported that silver and zinc load micro-arc oxidation layer on titanium exhibited excellent activity against *Escherichia coli* (*E. coli*) after a six-month immersion in physiological saline [124]. Another way to prolong the effective period of antimicrobials is to immobilize (or embed) them in the non-degradable implant surfaces and prevent release. Cao et al. developed a silver plasma immersion ion implantation and deposition (Ag PIII&D) procedure to in situ synthesis and immobilize silver nanoparticles (Ag NPs) on titanium surface [143]. The process is generally carried out in a vacuum chamber of about 2.5×10^{-3} Pa and takes a pure silver rod (10 mm in diameter) as a cathode to produce cathodic arcs, which serve as sources of positively charged silver ions (Ag^{n+}). The silver arcs are filtered by a curved magnetic duct to remove the macro-particles produced. The energetic silver ions in a plasma form are accelerated and injected in a non-line-of-sight manner onto the titanium surfaces, which are negatively biased by a pulsed high voltage synchronizing with the cathodic arc current under a certain frequency. The positively charged silver ions become neutral atoms when they reach the titanium surfaces. As the process continues, the neutral atoms are further condensed and nanoparticles precipitate. By using this process, well-distributed Ag NPs were synthesized and immobilized on titanium.

Table 5. Representative reports on long-term antibacterial surfaces.

Active Ingredients	Intended Use (Substrates)	Effective Period	Reference
Tigecycline, Copper ions	**Treatment for osteomyelitis (Alginate aerogel)**	**18 days**	[121]
Vancomycin	**Cement (Calcium phosphate)**	**168 days**	[122]
(Z-)-4-bromo-5-(bromomethylene)-2(5H)-furanone	**Dental implants (Titanium)**	**60 days**	[123]
Silver/Zinc ions	**An orthopedic and dental implant (Titanium)**	**180 days**	[124]
Nanosilver	**Bone implant (Polylactic acid fiber)**	**11 days**	[125]
Honokiol	**Remineralization of demineralized enamel (Poly(amido amine) (PAMAM) (Dendrimer)**	**24 days**	[126]
Patchouli Essential Oil	**Wound Dressing (Polyvinyl alcohol and chitosan)**	**2 days**	[127]
Cetylpyridinium chloride	**Endodontic sealers (Polyhydroxyethyl methacrylate trimethylolpropanetrimethacrylate)**	**48 days**	[128]

Active Ingredients	Intended Use (Substrates)	Effective Period	Reference
Metallic silver	**Hard tissue replacements (Titanium)**	**84 days**	[129]
Copper	**Orthopedics (Titanium)**	**14 days**	[130]
Zinc/Copper	**Cement (dicalcium silicate)**	**3 days**	[131]
Amoxicillin	**Wound dressing (Poly (e-caprolactone))**	**7 days**	[132]
Chlorhexidine	**Medical devices (not clear, 316L)**	**3 days**	[133]
Silver ions	**Orthopedic implants (Titanium)**	**189 days (silver release)**	[134]
Nanosilver	**Biomedicine (not clear)**	**7 days**	[135]
Nanogold/Titania	**Orthopedic implants (Titanium)**	**6 days**	[136]
Nanosilver	**Orthopedic implants (Titanium)**	**60 days**	[137]
Silver nanoparticles	**Orthopedic implants (Titanium)**	**60 days**	[138]
Poly (poly (ethylene glycol) dimethacrylate)	**Peritoneal dialysis catheters (Silicone)**	**30 days**	[139]

3.2. Response to pH Shifts

It is known that the pH shift is a common phenomenon of bacterial infections [144][145][146], laying the basis for the development of pH-responsive antibacterial surfaces. The antibacterial activity of pH-responsive films or coatings can be triggered by the protonation or deprotonation of their ionic groups. The thiazole and triazole groups, for example, in polymer PS54-b-PTTBM23 (on porous polystyrene surfaces) can be protonated under acidic pH levels, which increased the positive charge density on the materials surface to act against bacterial adhesion [147]. In addition, the killed bacteria can be further removed by increasing the pH levels (pH 7.4, for instance), which induced deprotonation of the thiazole and triazole groups in the materials [147]. Normally, pH-responsive surfaces are designed for the controllable release of antibacterial agents by manipulating the materials' pH-associated swelling or shrinking processes. By shifting the environmental pH, the protons of the carboxyl repeat units in poly(methacrylic acid) can be removed to make the material swell, which can control the release of antibacterial drugs [148]. In this manner, Wei et al. developed a pH-responsive surface capable of loading bacteriolytic lysozyme at acidic pH levels and releasing it under neutral or basic pH [148]. A pH-sensitive fibrous membrane was also developed to control the release of antibacterial gatifloxacin hydrochloride and silver nanoparticles [149]. The backbone (hydrophobic)-attached amino groups (weak basic moieties) of chitosan adapt to a deprotonated state above pH 6 while becoming protonated and positively charged at low pH, demonstrating a pH-dependent extension of the colloid chains and consequently swelling of the material [150]. Accordingly, chitosan was crosslinked with hydroxypropyl methylcellulose and 2-hydroxypropyl-β-cyclodextrin to produce a superabsorbent hydrogel for controllable delivery of antibacterial 3,4-dihydroxy cinnamic acid in response to pH changes [150]. Similarly, the structure of keratin hydrogel was reorganized by manipulating the protonation and deprotonation process of carboxyl groups in the material, yielding pH-dependent shrinking and swelling at low and high pH levels, respectively [151]. This behavior of the keratin hydrogel was taken to control the release of biocidal zinc oxide nanoplates in a pH-dependent manner, which can be a potential therapy response to a bacteria-contaminated media with biased pH and treatment of chronic wounds [152].

In addition, acid-labile bonds can also be used to program the release of antibacterial agents. Antibacterial gentamicin was conjugated with an alginate dialdehyde Schiff base reaction between the aldehyde groups (-CHO) and amino groups (-NH2) from the polymer, and was released due to the acidic environment triggered the disintegration of the Schiff base bonds [153]. Similarly, antimicrobial 6-Chloropurine was conjugated to 4-(vinyloxy) butyl methacrylate (VBMA) to produce 4-(1-(6-chloro-7H-purin-7-yl) ethoxy) butyl methacrylate (CPBMA), which contained a hemiaminal ether linkage can be hydrolyzed in mildly acidic conditions and allowed the controllable release of the antibacterial agent [154]. Moreover, pH-induced material structural evolutions, such as degradation, disintegration, and conformational changes, are also applied for the controllable delivery of biocides. Polyacetal-based polymers are degradable under acidic pH levels and possess a relatively low critical solution temperature (LCST) which allows wettability control by shifting the temperature (between LCST and room temperature) [155]. On account of this, a film-forming triple polymer-gel matrix containing polyacetal-based polymer was prepared by De Silva et al. to control the topical release of silver sulfadiazine, which was highly efficient against wound pathogens, such as *S. aureus*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Candida albicans* (*C. Albicans*) [155]. The Schiff base structure between the amino groups ($-NH_2$) in dopamine and the aldehyde groups (-CHO)

in oxidized dextran can be formed at pH 7.0 under the protection of nitrogen (N_2) [156]. The Schiff base bonds were disintegrated due to exposure to acidic bacteria-infected diabetic wounds, which was the mechanism used by Hu et al. to control the release of antibacterial silver nanoparticles by dopamine-conjugated oxidized dextran polymers [156]. The pH-induced conformational changes in silk fibroin (in a nanocapsule structure) were also applied to control the delivery of eugenol, which exhibited strong efficacy against both Gram-positive *S. aureus* and Gram-negative *E. coli* [157].

3.3. Response to Bacterial Charging

Membrane-bound respiratory electron transfer in bacteria plays a critical role in the synthesis of adenosine triphosphate and bacterial maintenance [158]; therefore, it can be a potential target for antibacterial surfaces. Extracellular electron transfer is a general mechanism required for bacterial growth [159][160][161][162]. The microbial cell envelope is not electrically conductive; hence bacteria have evolved strategies to exchange electrons with extracellular substances [163], including direct electron transfer via physical contacts (through the bacterial envelope or pili) between a microbe and a material surface, and redox-active compounds mediating electron shuttle between bacteria and the material's surface serve as electron acceptors [164].

Accordingly, Cao et al. proposed to construct antibacterial coatings targeting the extracellular electron transfer process in pathogenic bacteria [165][166]. Ag NPs in various sizes (4–25 nm) were in situ synthesized and immobilized onto plasma-spraying-prepared titanium oxide coatings by manipulating the atomic-scale heating effect in silver plasma immersion ion implantation. The antibacterial efficacy of the resulting composite coatings was dependent on the particle size and interparticle space of the immobilized silver, i.e., large particles (5–25 nm) induced fatal cytosolic content leakage and lysis of both Gram-negative and Gram-positive bacteria while small ones (~4 nm) did not [165]; and a relatively large interparticle space was superior to a small interparticle space is disrupting the integrity of the adherent bacterial cells [166]. Similar results were also reported in follow-up studies by using silver nanoparticles decorated with tantalum oxide coatings [167][168]. By using plasma spraying, graphene nanomaterials decorated with titania coatings were prepared for antibacterial applications [169]. The coatings can collect the electrons extruded by adherent bacterial cells due to the rectification of the Schottky-like graphene-titania boundaries [169]. In vitro evidence showed that cobalt-titanium dioxide and cobalt oxide (CoO or Co_3O_4)-titanium dioxide nanoscale heterojunctions can downregulate the expression of respiratory gene levels in bacteria and cause oxidative damage to bacterial surfaces [170]. In another study, Wang et al. also found that the antibacterial efficacy of tungsten-incorporated titanium dioxide coatings (prepared by micro-arc oxidization) was related to their strong capability in the storage of bacteria-extruded electrons and accumulation of sufficient valence-band holes inducing oxidative damages to the microbes [171]. These findings have opened up new avenues for taking advantage of the intrinsic feature of biological systems to design and control the antibacterial actions of biomaterials.

3.4. Response to Light Irradiation

Sterilizing materials' surfaces with ultraviolet (UV) light is a well-established standard method that has been around for decades. Materials converting light energy to heat for local disruption of bacterial colonization, i.e., photothermal therapy, are promising alternatives to antibiotics that possibly circumvent the problem of resistance [172]. Gold nanoparticles have been studied widely because of their high efficiency of photothermal conversion via surface plasmon resonance in the near-infrared (NIR) region (in the range of 700–1100 nm) [173]. It was reported that a gold nanoparticle and phase-transitioned lysozyme hybrid film was able to kill 99% of adherent bacteria within 5 min under the illumination of a NIR laser [173]. Composite thin films were produced by coordinative assembly of tannic acid (TA) and iron ions (Fe^{3+}) and yielded Au-TA/Fe [174]. These films exhibited high absorption and efficient light-to-heat convention under NIR irradiation, as a result, they had efficient photothermal killing effects that disrupted 99% of adherent microbes, including both Gram-negative *E. coli* and Gram-positive MRSA strains.

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