Emerging technologies for long-term antimicrobial device coatings: advantages and limitations

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Impact statement

This work provides an overview, with advantages and limitations of the most recently developed antibacterial coating technologies, enabling other researchers in the field to more easily determine which technology is most advantageous for them to further develop and pursue.

Abstract

Over the past 20 years, the field of antimicrobial medical device coatings has expanded nearly 30-fold with technologies shifting their focus from diffusion-only based (short-term antimicrobial eluting) coatings to long-term antimicrobial eluting and intrinsically antimicrobial functioning materials. A variety of emergent coatings have been developed with the goal of achieving long-term antimicrobial activity in order to mitigate the risk of implanted device failure. Specifically, the coatings can be grouped into two categories: those that use antibiotics in conjunction with a polymer coating and those that rely on the intrinsic properties of the material to kill or repel bacteria that come into contact with the surface. This review covers both long-term drug-eluting and non-eluting coatings and evaluates the inherent advantages and disadvantages of each type while providing an overview of variety applications that the coatings have been utilized in.

Keywords: Polymer, drugs, bacteria, biomedical, chronic, cardiovascular

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Introduction

Severe infections can develop surrounding a variety of implanted medical devices such as hernia meshes, orthopedic implants, catheters, and vascular grafts. Recent changes in healthcare reimbursement policy have shifted the cost of implant infections back to the original service provider as a ''preventable infection,'' generating an urgent need to develop devices better able to prevent bacterial and fungal infections.[1]

The severity of the infection depends upon the type of bacteria or fungi involved as well as the maturity of the biofilm they may develop upon bacterial/fungal colonization on the device. In particular, Gram-positive *Staphylococcus aureus* (*S. aureus*) and *epidermidis* (*S. epidermidis*) are some of the most common bacterial strains responsible for forming biofilms on the devices.[2–4] For fungal biofilms, *Candida albicans* (*C. albicans*) is the most prevalent.[5] Once the biofilms are established, they can be very difficult to treat with conventional antibiotic treatments since the bacteria in the biofilm are metabolically inactive, rendering the biofilms less responsive to antibiotics.[6–8] Under these circumstances, the infected device often fails and must be removed from the patient to eradicate the infection. Therefore, the goal of antimicrobial device coatings is to prevent the infection, since treatment after infection occurs is challenging. While only a small percentage of patients develop infections, the cost of treating these infections surpasses $11 billion annually with nearly 2 million infection cases annually.[9]

In an attempt to mitigate the infections associated with the implanted devices, a variety of antimicrobial device coatings have been developed with the goal of inhibiting the growth of biofilms on the devices both with and without drugs. Antimicrobial device coatings have dramatically evolved over the past couple of years. While early technologies focused on diffusion-based antibiotic-eluting coatings that provide short-term antimicrobial therapy, recent technologies have shifted their focus to coatings with more long-term antibiotic-eluting capabilities and materials that show intrinsic antimicrobial activity. Figure 1 depicts the growing trend in the annual number of scientific journal publications on antimicrobial coatings over the past 17 years.[10] Specifically, from 1997 to 2014, there has been a nearly 30-fold increase in the number of articles annually published on antimicrobial coatings, demonstrating the large number of innovations that have recently been developed in the field. In particular, the increase in publications over the past five years can be partially attributed to the legislative changes of the Patient Protection and Affordable Care Act (2010).[1]

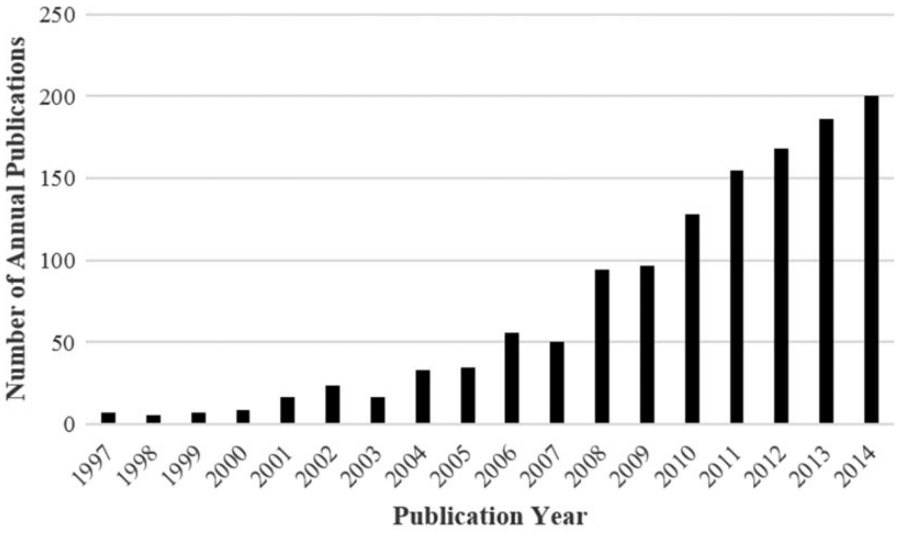

Figure 1 Trend of the number of peer-reviewed scientific journal articles on antimicrobial coatings annually published since 1997 (Archived on PubMed).[10]

Many of the coatings rely on the encapsulation of various antibiotics or antifungal drugs to prevent device infection by locally delivering the drug.[5,11–34] While there are many benefits to locally delivering the drug to prevent device infection, these coatings have the potential to cause off-target long-term toxicities, and can lead to the development of drug-resistant bacteria when the antibiotic is delivered at a subinhibitory dose and has a limited window of activity.[35] In an effort to extend the duration of the release and enhance the loading of the encapsulated drugs beyond that capable of ordinary polymers, many coatings have started to incorporate high-affinity moieties such as cyclodextrin (CD). CDs are cyclic oligosaccharides with a hydrophilic exterior and a hydrophobic interior that enable the encapsulation of hydrophobic drugs through the formation of a drug-inclusion complex.[18] The use of CD polymers is particularly desirable in device coatings because they have been shown to increase antibiotic loading in devices 10-fold[36] and have shown *in vitro* stability for nearly eight months[37] and controlled *in vivo* delivery for 28 days.[11,38]

Alternatively, other groups have taken another approach altogether to reduce these detrimental effects yet still obtain antibacterial device coatings. Specifically, many groups have worked on developing metallic-based[39–43] and polymer-based[35,44–47] non-drug-eluting coatings. The advantage of these coatings is that they intrinsically possess antibacterial and antifungal properties without the use of drugs and have the potential for much longer lasting applications than drug-eluting coatings.[45]

In this paper, an overview of affinity-based device coatings will be presented along with a review of non-drug approaches for antibacterial coatings.

Antibiotic-eluting device coatings

Introduction to affinity-based antibiotic-eluting device coatings

Affinity-based drug-eluting device coatings have been used in a wide variety of applications. CD has been incorporated into hernia mesh coatings, orthopedic coatings, catheter coatings, and vascular graft coatings. Figure 2 outlines the primary applications in which CD is used as an antimicrobial coating for medical devices. The goal of affinity-based coatings is to extend the delivery timeline of encapsulated antimicrobial drugs to treat advanced infections and prevent the formation of biofilms. Many infections are not completely eradicated by a single bolus dose of antibiotics and require many doses over an extended period of time to ensure that all bacteria are eradicated and to avoid generation of drug-resistant bacteria. CD is a desirable molecule to incorporate into these coatings because it has the ability to form drug-inclusion complexes with many small molecule hydrophobic drugs, thereby minimizing the effects of a ''burst'' release of the drug from the coating and providing therapeutic doses of the drug over extended periods of time.[18] This is an improvement over traditional delivery systems that rely only on diffusion to get drug out of the polymer and lack the additional affinity interactions between the polymer and drug. When diffusion is the primary mechanism of drug release, it can often result in a majority of the loaded drug being released over a very brief period of time which is not desirable for many antibacterial applications.

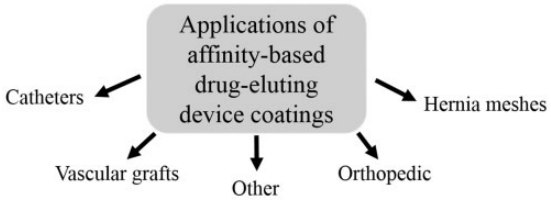

Figure 2 Some of the ubiquitous applications of affinity-based cyclodextrin device coatings include catheter, vascular graft, orthopedic, and hernia mesh coatings

Hernia and soft-tissue applications

Hernia meshes are the current standard of care for abdominal hernia repair surgeries.[48] They have been shown to

shorten hospital stays and result in fewer revision surgeries compared with non-mesh treatments.[48] However, there are many potential complications that can result from hernia meshes (i.e. seromas, adhesions, mesh migration, and infections).[48] Hernia mesh infections occur in approximately 10% of more than 1 million soft tissue repair procedures.[48] If an infection is to develop, it can compromise the entire repair surgery and often requires systemic antibiotic treatment and in some cases removal of the mesh.[48] To repair hernias, physicians typically use either a laparoscopic or open procedure. Several studies have been conducted to evaluate whether the non-invasive (laparoscopic) or the more invasive (open) procedure resulted in fewer infections.[48] However, it was found that the risk of infection was still very prevalent following both approaches and that the risk also depends on the material and positioning of the mesh.[48] Therefore, techniques such as coating the meshes with affinity-based polymers have been explored to reduce the infection rate.[11,17,18,36,49]

Coating hernia meshes with CD has resulted in a 10-fold increase in antibiotic loading capacity[36] and an *in vivo* delivery of 28 days.[11] Polyester,[11,18] polyamide,[36] and polypropylene[17] meshes have all been successfully grafted with CD in order to deliver vancomycin[11] and ciprofloxacin.[17,36] The antibiotic-loaded coatings have demonstrated broad-spectrum antibacterial activity against *S. aureus*, *S. epidermidis*, and *E. coli*.[36]

Several techniques have been used to graft CD onto the meshes. To graft CD onto polyamide meshes, El Ghoul *et al*.[36] used citric acid as a cross-linking agent. The resulting fibers demonstrated an increased hydrophilicity and improved biocompatibility compared with unmodified meshes.[36] For polypropylene meshes, Laurent *et al*.[17] used polycarboxylic acid to cross-link hydroxypropyl-gamma-CD to the mesh. Hydroxypropyl-gamma-CD was selected due to its high affinity for ciprofloxacin and increased reactivity.[17] Since it has an increased reactivity, milder reaction conditions can be used to graft it to the mesh that can help to protect the mesh from degradation.[17] Additionally, the reaction has the potential to be implemented on an industrial scale.[17]

Orthopedic applications

Orthopedic implants such as joint replacements and fracture fixations require the use of several different materials to restore mechanical function such as titanium, bone cement (poly(methyl methacrylate)) (PMMA), and stainless steel that all have the potential to become infected. Nearly 1 million knee and hip joint replacements were completed in 2010 and approximately 1–4% of these cases developed infections.[50,51] If untreated, these infections have the potential to develop into severe infections such as osteomyelitis.[52] These cases can be particularly challenging to treat and can often result in the loss of significant bone structure due to the effects of osteolysis.[52] To prevent infections, CD has frequently been used as an orthopedic implant coating.[16,18,29,31,53–56] Specifically, it has been used in conjunction with hydroxyapatite to promote osseointegration.[29,31,53,56] These applications were able to show sustained antibiotic release from CD over 150–300 h,[18,53] enhanced bacteriostatic activity and osteoblast cytocompatibility,[16,29] and were able to inhibit the growth of *S. aureus* over 28 days.[18] Figure 3 shows the typical setup of a zone of inhibition assay that is used to evaluate the daily antibacterial activity of the loaded devices.

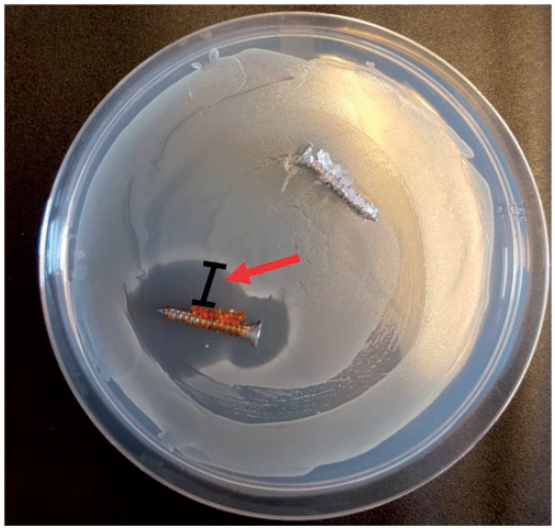

Figure 3 Standard set-up for a zone of inhibition assay in which a CD-coated stainless steel screw loaded with antibiotic (left) and CD coated control screw (right) are placed on a fresh lawn of S. aureus bacteria overnight, the zone of inhibition is recorded (indicated by red arrow), and the screws are transferred to a fresh plate. The coated control screw (no drug) does not show any zone of inhibition. (A color version of this figure is available in the online journal.)

Catheter applications

Urethral catheters are typically used to drain a patient's bladder and are used in approximately 25% of patients in hospitals.[14] In many cases, the catheters are only used for a short period of time (i.e. 1–14 days); however, for chronic bladder dysfunction, catheters can be used for up to four to eight weeks.[14] Catheter infections are a major clinical concern that are primarily caused by *E. coli* with over 100,000 catheter-associated urinary tract infections developed annually.[14] Historically, polymer coatings on catheters have been unsuccessful for long-term antibiotic therapy due to harsh flow conditions.[14] Therefore, the mechanical properties and robustness of the antimicrobial coating are particularly critical in catheter applications.

To reduce the risk of catheter infections, CD has been successfully used as a coating for catheters.[5,19,57] The benefits of grafting CD to the surface are two-fold; CD demonstrates enhanced hemocompatibility and is able to form an inclusion complex with the antifungal agent miconazole.[5] Specifically, CD has been grafted onto both polyethylene and polypropylene surfaces through a reaction with glycidyl methacrylate using oxidative gamma-ray preirradiation.[5,19] The use of glycidyl methacrylate enables a stable grafting of CD to the surface of the catheter due to the reaction between the epoxide group on glycidyl methacrylate and hydroxyl group of CD forming a stable covalent bond.[5,19] Nava-Ortiz *et al.* were able to demonstrate that

CD-functionalized catheters were capable of releasing active miconazole significantly reducing *C. albicans* biofilm formation.[5]

In another application, Iordache *et al.* coated silicon with gamma-CD/usnic acid thin films using the Matrix Assisted Pulsed Laser Evaporation (MAPLE) technique.[57] The MAPLE technique enables the formation of a smooth and uniform coating on the material.[57] By combining the effects of usnic acid and CD, they were able to achieve an antibacterial coating effective against several different strains of Gram-positive bacteria (i.e. *S. aureus*, *Enterococcus faecalis*, and *Enterococcus faecium*) that were biocompatible and demonstrated long-term controlled release of the antibiotic.[57]

Vascular graft applications

Vascular graft-related infections occur in approximately 6% of patients.[13] These infections are particularly dangerous if they are localized at the aorta because they can lead to mortality in 50% of the cases.[13] If the infections go untreated, they can lead to additional surgeries and in some advanced cases even amputation.[21] The most common pathogens associated with these infections are *S. aureus*, *S. epidermidis*, and *E. coli*.[21] Current therapy for these infections involves systemic antibiotic administration; however, it is generally unsuccessful in preventing recurrent infections and can lead to other downstream tissue toxicities and the development of drug-resistant bacteria.[21] Previous methods to reduce the risk of infections involved coating the graft with either collagen, gelatin, or other hydrogels and loading an antibiotic.[13] However, these methods have been unsuccessful in providing a long-term release of the antibiotic since the coating typically degrades after only a couple of days.[13]

To develop a more robust coating capable of long-term controlled delivery of antibiotics, CD has been successfully integrated into vascular graft coatings.[13,21,24,32–34,56–60] Specifically, polyester grafts have been coated with CD (both β-CD and methylated β-CD) via a polyesterification reaction between CD and citric acid.[13,24] Ciprofloxacin has been encapsulated into the CD coatings, and Blanchemain *et al.*[13] have demonstrated that the modified coatings were capable of extending the duration of the release of ciprofloxacin six-fold compared with the unmodified coatings. Similarly, Jean-Baptiste *et al.*[21] coated polyester grafts with CD using polycarboxylic acid and demonstrated sustained release of antibiotics (i.e. rifampin, vancomycin, and ciprofloxacin) both *in vitro* and *in vivo* against six different bacterial strains. Additionally, hydroxypropyl-β-CD has been used in order to prolong the delivery of antibiotics and has demonstrated reduced renal toxicity compared with other CD formulations.[59] This specific coating was capable of inhibiting bacterial growth for seven days and remained intact *in vivo* for a month following implantation.[59]

In another application, polyethylene terephthalate (PET) vascular grafts were coated with CD using polycarboxylic acid and impregnated with vancomycin.[32] The coating demonstrated no significant cytotoxicity and was capable of releasing the antibiotic in a controlled manner over 50 days.[32] Additionally, Blanchemain *et al.*[33,34] demonstrated that CD coatings were mechanically robust and capable of withstanding both longitudinal and circumference traction supporting their efficacy for clinical use.

Summary

Affinity-based drug-eluting coatings have been successfully developed for a wide variety of medical applications and have demonstrated enhanced loading capabilities as well as sustained antibacterial activity against a broad-spectrum of bacteria. Despite many of the coatings relying on the use of antibacterial or antifungal drugs to inhibit the formation of biofilms, the antibacterial activity of these coatings is comparable to many metallic and polymeric coatings with intrinsic antibacterial activity (see Non-drug eluting coatings section), since they are capable of long-term delivery of the drug. Additionally, CD has been shown to be capable of loading antibiotics through mature biofilm that has developed on its surface, thereby demonstrating its efficacy as a long-term antimicrobial coating, capable of reloading once all of the initial loaded drug has been released.[60] However, some concerns still exist regarding the use of antibiotics or antifungal drugs since long-term usage can lead to the development of drug-resistant bacteria and downstream tissue toxicities.[35]

Non-drug eluting coatings

Introduction

To mitigate the concerns and limitations associated with drug-eluting antibacterial device coatings, several different types of coatings have been developed that rely on the intrinsic ability of the material (i.e. metal or polymer) to repel or inhibit the growth of bacteria on its surface. Figure 4 depicts some of the different antimicrobial mechanisms of action of the two primary classes of non-drug-eluting coatings. Table 1 outlines many of the common specific compositions of metallic and polymer-based antimicrobial coatings.

Metallic-based coatings

Many successful metallic-based coatings have been developed using silver, titanium, zinc, and copper nanoparticles.[39–43,61–67,73–75,81–83,86–94] Most of these applications involve leaching metallic ions in order to disrupt the membrane of bacteria and prevent the proliferation of bacteria on the surface of the device. Specifically, silver ions are capable of interacting with and disrupting the mitochondrial respiratory chain of bacteria, directly impacting ATP production and leading to DNA damage in the bacteria.[81] The primary limitation of these coatings is that they need to release an effective concentration of metallic ions to eradicate bacteria that is simultaneously low enough to prevent downstream tissue toxicities.

Silver nanoparticle coatings. Silver ions have historically been used in antibacterial applications due to their ability to penetrate bacterial cells and cause damage to both the membrane of the cell and enzymes within the cell.[42] To capitalize

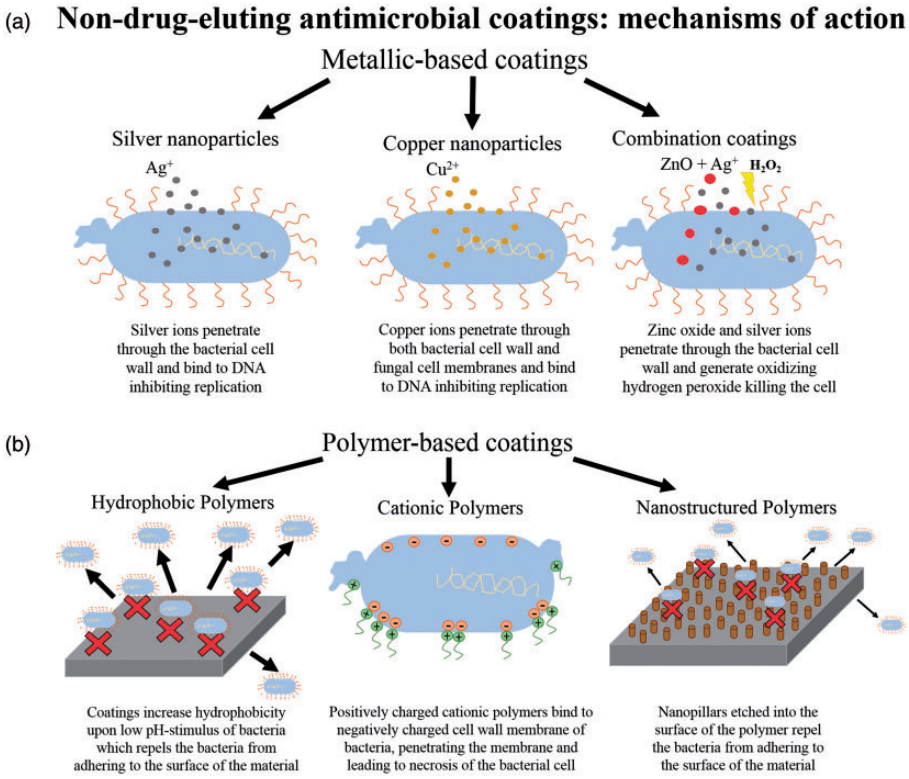

Figure 4 Overview of the different antimicrobial mechanisms of action of different non-drug-eluting metallic and polymer-based coatings. (A color version of this figure is available in the online journal.)

Table 1 Overview of different varieties of non-drug eluting antimicrobial device coatings

Metallic-based coatings	Polymer-based coatings
Silver nanoparticles	Quaternary ammonium salts
-Silver nanoparticles with metal oxides[39,40,43,61,62]	*-Functionalized QASs*[44,68,69]
-Silver doped hydroxyapatite[63,64]	*-Imidazolium salts*[70,71]
-Nanosilver coatings[42,65,66,67]	*-QAS silane coating*[35]
	-QAS crosslinked PEI nanoparticles[47]
	-Rubber oligomers with QAS groups[72]
Capped silver nanoparticles	Cationic polymers
-Kocuran capped silver glyconanoparticles[73]	*-PEI brushes*[45]
-Cyclodextrin-capped silver nanoparticles[74]	*-Cationic pyridinium*[76]
-PEG-heparin-capped silver nanoparticles[75]	*-Cationic PEG polycarbonate diblock copolymers*[77,78]
	-Cationic copolymers with QAS groups[79,80]
Silver-loaded nanocomposites	Nanotopography-etched surfaces
-Poly(styrene-co-acrylic acid) nanocomposites[81]	*-Nanopillar etching*[84]
-PNIPAm microgels[82]	*-Biological mimicking surface*[85]
-Spherical polyelectrolyte brushes[83]	
Copper nanoparticles	pH-sensitive hydrophobicity
-Copper nanocomposites[86]	*-Hydrophobic/hydrophilic diblock copolymer*[25]
-Copper and silver nanoparticles[41,87]	*-Layer-by-layer hydrogel*[46]
-Copper nanoparticles with metal oxides[88,89]	

on the intrinsic antibacterial activity of silver ions, several groups have worked to directly incorporate silver nanoparticles into their antibacterial coatings.[42,63–67,73–75,81–83] These coatings have shown activity against both *E. coli* and *S. aureus*,[64,65] minimal cytotoxicity,[42] and promoted the formation of carbonated hydroxyapatite.[66]

Beyond these applications, silver nanoparticles have been incorporated into antibacterial coatings using

poly(styrene-co-acrylic acid),[81] poly(N-isopropylacrylamide) (pNIPAm),[82] poly(N-vinylcarbazole)-poly(acrylic acid),[83] and hydroxyapatite.[63,64] Specifically, poly(styrene-co-acrylic acid) has been used to load silver ions and showed broad-spectrum coverage against both *E. coli* and *S. aureus*.[81] Similarly, pNIPAm has been utilized as an antibacterial thermoresponsive coating (activated by pH, light, or temperature) in combination with silver nanoparticles and has shown efficacy against both *E. coli* and *Bacillus subtilis*.[82] Additionally, poly(N-vinylcarbazole)-poly(acrylic acid) spherical polyelectrolyte brushes have been used to encapsulate silver nanoparticles in a layer-by-layer assembly.[83] Liu *et al.*[83] were able to demonstrate that these coatings were capable of long-lasting antimicrobial activity against *E. coli* and that significantly more silver nanoparticles could be immobilized in the coating through repeat loadings.

To overcome some of the toxicities associated with free metallic ions, various capping agents have been used such as Kocuran,[73] PEG-heparin hydrogels,[75] and β-CD.[74] Kocuran is an exopolysaccharide that functions as both a capping and reducing agent.[73] Specifically, Kocuran assists in the creation of hydroxyl radicals that ultimately are bactericidal towards both *E. coli* and *S. aureus*.[73] Kumar *et al.*[73] have demonstrated that Kocuran-capped silver nanoparticles have an enhanced antibacterial activity compared with non-modified silver nanoparticles due to the exopolysaccharide's ability to penetrate bacterial membranes. Silver nanoparticles have also been capped with PEG-heparin hydrogels to improve the hemocompatibility of the coating.[75] Fischer *et al.*[75] have demonstrated that these multilayer coatings were capable of long-term antibacterial activity against *E. coli* and *S. epidermidis* and did not invoke undesired hemolysis, platelet activation, or plasma coagulation. Beta-cyclodextrin (β-CD) has also been utilized as a capping agent to stabilize silver nanoparticles.[74] Jaiswal *et al.* demonstrated that β-CD-capped silver nanoparticles were less cytotoxic towards HaCaT cells, since CD reduced the number of reactive oxygen species that are responsible for causing the oxidative stress.[74] Additionally, they demonstrated that β-CD was capable of enhancing the antibacterial activity of the nanoparticles against planktonic bacteria such as *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa*.[74]

Copper nanoparticle coatings. As an alternative to traditional silver-based coatings, copper nanoparticles have also been used. Silver demonstrates a strong antibacterial effect on prokaryotes (i.e. bacteria), whereas copper has a stronger effect on eukaryotes such as fungi.[86] Therefore, to develop a non-drug eluting coating capable of preventing the growth of fungal biofilm, Cioffi *et al.*[86] electrochemically synthesized a copper nanoparticle coating in an alkyl ammonium micellar solution. The nanoparticles were composed of two layers: an inner copper oxide layer and outer shell of either polyvinylmethylketone (PVMK), polyvinylchloride (PVC), or polyvinylidenefluoride (PVDF).[86] The colloid suspension of nanoparticles was then spin-coated onto glass plates.[86] The coatings were shown to be capable of inhibiting growth of *Saccharomyces cerevisiae* yeast and that the antifungal effect was dependent upon the concentration of copper nanoparticles in the coating.[86] The primary concern with these coatings is that copper ions are especially toxic to human cells, so it is critical to control how many ions are being released to inhibit fungal growth.[86]

In another application, Slamborova *et al.* combined both silver and copper in a coating in order to provide long-term broad-spectrum antibacterial (i.e. methicillin-resistant *S. aureus* (MRSA)) and antifungal coverage.[89] The coatings were prepared using a sol-gel method with silver and copper ions and titanium dioxide nanoparticles.[89] The sol-gel method is particularly advantageous because it enables a coating to form that does not crack easily.[89] They were able to demonstrate that the coating was effective against seven different bacterial strains (i.e. *E. coli*, *S. aureus*, MRSA, MRSA-2, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*) highlighting the overall broad-spectrum coverage and versatility of the coating.[89] Additionally, the coatings were found to be very robust and capable of withstanding up to 150 wash cycles without losing their integrity.[89]

Combination coatings. Hybrid coatings have also been developed combining different metallic ions and metal oxides.[39,41,43,61,62,87–91] By combining several materials, different groups have developed antibacterial coatings that are anticorrosive,[39,43] titanium dioxide has also been combined with both silver nanoparticles and zinc oxide (ZnO) to improve the broad-spectrum antibacterial coverage of the coating.[61,62] Selvam *et al.* demonstrated that the ZnO in these coatings performed better against both *S. aureus* and *E. coli* than the TiO_2 and silver nanoparticles alone.[61] It is hypothesized that the ZnO enhances the antibacterial activity because it readily permeates bacterial membranes through the generation of hydrogen peroxide.[62] Furthermore, TiO_2 has been combined with copper to form antifungal coatings on titanium.[88]

Summary. Metallic-based antibacterial coatings are versatile alternatives to traditional antibiotic-eluting coatings. They are particularly advantageous in reducing the risk of developing drug-resistant bacteria and have the potential for long-term antibacterial activity. By combining several different metal ions, they can be tailored to have broad-spectrum antibacterial and antifungal activity. They can also be customized to promote osseointegration and are typically very biocompatible. However, there are some drawbacks associated with metallic-based coatings. Specifically, these coatings leach metallic ions continuously throughout the body, which in high concentrations can be lethal to mesenchymal stem cells, lymphocytes, and monocytes.[63] Additionally, silver nanoparticles can accumulate in tissues throughout the body and cause long-term damage.[42] They have been found to accumulate in the liver, spleen, brain, and skin and have the ability to cause oxidative damage to cells.[42]

Polymer-based coatings

Many successful polymer-based coatings have been developed using different quaternary ammonium salts and cationic polymers.[25,35,44–47,68–72,76–80,84,85,95–101] These coatings primarily function through either a disruption of the bacterial membrane using cationic charges or hydrophobic interactions repelling the adherence of bacteria. The benefit of these coatings is that they are primarily non-leaching coatings and therefore demonstrate long-term intrinsic antibacterial activity, are biocompatible, and do not cause any significant cytotoxicity.

Quaternary ammonium/imidazolium salts. One of the most frequently used polymer coating is derived from quaternary ammonium salt groups (QAS) that have well-known antibacterial activity.[35,44] In these applications, QASs are grafted onto the material's surface and function as a chemically anchored biocide.[44] The benefits of this technique are that the polymer does not leach off into the patient's systemic circulation, the antibacterial activity of the coating has the potential to last longer than drug-eluting coating, and you are able to achieve a high concentration of localized antibacterial activity.[44] QASs have been grafted onto polyurethane using acetic acid through an acidification reaction on the tertiary amine groups of the polyurethane[44] and through vapour-phase plasma-induced graft-polymerization.[35] The QAS-coated catheters have demonstrated sustained activity against *E. coli*.[35] Additionally, Bakhshi *et al.*[44] have demonstrated that the coatings do not show any significant cytotoxicity towards fibroblasts and that they are capable of a 95% reduction in both *E. coli* and *S. aureus*.

Other salt-based antibacterial polymer coatings have used allylimidazolium salt that is grafted onto the material via a thiol-ene photocuring reaction.[70] Kim *et al.*[70] have demonstrated that the photocuring method enables the coating to uniformly coat the surface of the material and that the antibacterial activity (against *E. coli* and *S. aureus*) of the coating was dependent upon the concentration of allylimidazolium salt. Similarly, Izmaylov *et al.*[71] grafted three different imidazolium salts to cotton fabrics to create antibacterial coatings. The salts were linked to the fabric by either ionic or covalent bonds using siloxane oligomers as the coupling agent.[71] These coatings were capable of greater than a 97% reduction of *S. aureus* and a nearly 50% reduction of *E. coli*, demonstrating their broad-spectrum activity and retained their antibacterial activity after four washing cycles.[71]

Cationic polymers. Beyond QASs, different cationic polymer brushes such as polyethyleneimine (PEI) have been grafted onto polyurethane catheters to prevent bacterial adhesion and biofilm formation.[45] The rationale behind using cationic polymers is that they are capable of penetrating the negatively charged membranes of bacterial cells ultimately causing necrosis.[76] Specifically, Gultekinoglu *et al.*[45] modified the PEI brushes with bromohexane to improve their ability to disrupt bacterial membranes. The grafted materials were capable of inhibiting the growth of *Klebsiella pneumonia*, *E. coli*, and *Proteus mirabilis* and demonstrated no cytotoxicity.[45] Different copolymers have also been used such as PEG-*b*-cationic polycarbonate to coat silicone catheters.[77] Specifically, Ding *et al.*[77] utilized a ring-opening polymerization technique to form the coating and demonstrated that the copolymer was capable of inhibiting the growth of *S. aureus* for over seven days. The coating was optimized to have the correct ratio of hydrophilicity to hydrophobicity in order to have the most antibacterial activity and did not demonstrate any significant cytotoxicity or hemolysis.[77] Alternatively, Altay *et al.*[76] have used cationic pyridinium polymers synthesized using a ring-opening metathesis polymerization reaction to form antibacterial coatings. They demonstrated that these cationic polymers with a hexyl unit were capable of killing 99% of *E. coli* colonies on the surface of a material within 5 min.[76] Additionally, they were able to conclude that the hydrophobicity of the surface was directly correlated to the antibacterial activity of the coating.[76]

To improve the hemocompatibility of cationic polymer coatings, molecules such as heparin have also been incorporated.[101] Specifically, Follmann *et al.*[101] developed a multilayer coating composed of *N*-trimethyl chitosan and heparin. This coating was capable of killing *E. coli* and served as both an antiadhesive and antibacterial coating.[101]

Combination QAS and cationic polymers. Other groups have developed coatings that combine both QAS groups and cationic polymers in order to create more robust coatings with broad-spectrum antibacterial activity. Atar-Froyman *et al.*[47] developed a crosslinked quaternary ammonium PEI nanoparticle coating. Significantly, their coating was capable of long-term antibacterial activity (one month) against *C. albicans*, *E. faecalis*, *S. mutans*, *S. aureus*, *P. aeruginosa*, and *S. epidermidis* both *in vitro* and *in vivo*, demonstrating the scope of its broad-spectrum activity.[47]

Beyond crosslinked PEI nanoparticles, other groups have utilized polymers such as *cis* 1,4-polyisoprene (i.e. natural rubber) with quaternary ammonium groups[72] and copolymers such as 4-vinyl-*N*-hexylpyridinium bromide with dimethyl(2-methacryloyloxyethyl phosphonate)[79] and poly(sulfobetaine methacrylate) with *N*-[(2-hydroxy-3-trimethylammonium)propyl] chitosan chloride[80] for antimicrobial coatings. In these applications, the combined use of QAS groups with cationic polymers enabled the coatings to demonstrate an increased level of antibacterial activity two orders of magnitude higher than uncoated surfaces.[80]

Other polymers. A variety of other innovative polymers have been developed as antimicrobial coatings such as hydrogels with a pH-triggered hydrophobicity.[46] The coatings comprised several hydrogel poly(2-alkylacrylic acid) films with different hydrophobicities (i.e. polymethacrylic acid, poly(2-ethylacrylic acid), poly(2-n-propylacrylic acid), and poly(2-n-butylacrylic acid)).[46] When the hydrogels are exposed to bacteria-induced acidification, they will become hydrophobic and antibacterial.[46] As the acidity increases (i.e. more bacteria present), the hydrogel's hydrophobicity increases enhancing its antibacterial activity.[46]

Table 2 Summary of the advantages and limitations of each primary classification of antimicrobial device coatings.

Classification of coating	Advantages	Limitations
Affinity-based antibiotic-loaded CD coating	-Long-term and controlled antimicrobial activity -Broad-spectrum antimicrobial activity -Antibacterial activity comparable to many non-drug-eluting coatings -Ability to load antibiotics into CD through mature biofilm	-Relies on use of antibiotic to inhibit formation of biofilm -Long-term antibiotic use can lead to development of drug-resistant bacteria -Downstream tissue toxicities from antibiotic use
Intrinsic antimicrobial metallic coating	-Reduce risk of developing drug-resistant bacteria -Long-term antimicrobial activity -Can be tailored for broad-spectrum activity -Can be customized to promote osseointegration	-Coatings leach metal ions continuously throughout body -In high concentrations, metal ions are cytotoxic -Metal nanoparticles can accumulate in tissue and cause long-term oxidative damage to cells
Intrinsic antimicrobial polymeric coating	-Coatings do not leach any compounds into the body (i.e. metal ions or drugs) -Many are biocompatible -Long-lasting antimicrobial activity -Minimize risk of developing drug-resistant bacteria -Robust coatings -Can be tailored for broad-spectrum activity	-Some varieties simply repel the bacteria from the surface of the material rather than completely eradicating it -New polymers could have compatibility issues

These coatings were successfully able to inhibit the proliferation of *S. epidermidis* and were not cytotoxic towards osteoblasts.[46]

Additionally, several polymeric coatings have been developed that rely on nanotopography for their antibacterial activity.[84,85] Specifically, Serrano *et al.*[84] developed both polypropylene and poly(ethylene terephthalate) nanotopographic coatings using oxidative plasma treatments. They were able to demonstrate that the nanostructures on their materials were capable of preventing the adherence of *E. coli*, but were not capable of killing bacteria on contact.[84] The rationale of nanostructured coatings is that the nanopillars formed on the surface of the material repel the attachment of bacteria to prevent the formation of biofilms.[84] However, the primary disadvantage with this technique is that the surface simply repels the attachment of the bacteria rather than directly killing the bacteria.[84] Similarly, Trentin *et al.* used a naturally occurring polyphenols (i.e. proanthocyanidins) as a coating in order to develop a coating with a nanotopography that mimics natural antifouling surfaces.[85] This coating was capable of inhibiting the attachment of *S. epidermidis*, *S. aureus*, and *E. faecalis* and is particularly advantageous in preventing the development of drug-resistant bacteria.[85]

Summary. A variety of polymer-based intrinsic antibacterial coatings have been developed that either function to repel the attachment (via hydrophobicity or nanotopographies) or directly kill bacteria that come in contact with the surface of the biomaterial (via cationic interactions) (Table 2). Polymer-based coatings are particularly advantageous because they do not leach any compounds into the body (i.e. metal ions or drugs) and are therefore typically very biocompatible and demonstrate long-lasting antibacterial activity while minimizing the risk of the development of drug-resistant strains of bacteria. Additionally, the coatings can be tailored for broad-spectrum antibacterial activity and are typically very robust. While these coatings offer many advantages over alternative coatings, some varieties do not kill the bacteria surrounding the implant but simply repel it. In some applications, this is sufficient; however, often it is necessary to completely eradicate the bacteria to prevent its proliferation instead of repelling it.

Future research

Overall, in this review several different varieties of antimicrobial medical device coatings have been explored. While each of the varieties has its advantages and disadvantages in regards to its robustness, length of antibacterial activity, and biocompatibility, none of them are completely efficacious for all applications. Many of the technologies explored in this review are still relatively new and therefore much more research need to be completed to improve upon these coatings to improve the duration of their antibacterial activity and robustness while minimizing the risk of developing antibiotic-resistant bacteria. Additionally, a majority of the technologies have only been tested in *in vitro* settings; therefore, there is a need to translate the successful *in vitro* studies into *in vivo* models and eventually clinical trials so that they can ultimately be implemented in a clinical setting. As legislation changes are placing increased emphasis on infection prevention, the need for long-lasting antimicrobial coatings will continue to become more prevalent.

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DECLARATION OF CONFLICTING INTERESTS

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