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Antibacterial biomaterials in orthopaedics

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Abstract

Implant infection is a serious complication resulting in pain, mortality, and antimicrobial resistance (AMR). AMR is one of the greatest challenges of the 21st century causing an estimated 25000 deaths/year in the EU at €1.5 billion/year in healthcare and productivity cost. By 2050, WHO estimates 10 million lives a year will be at risk from AMR, surpassing cancer, with $100 trillion in economic costs if no proactive solutions are found. The risk-of-infection associated with surgical implants is the one that is called for the highest attention. Antibacterial biomaterials are rapidly emerging as a primary component of the global mitigation strategy against both implant infection and AMR. As a result of extensive research efforts, advances are being made both on antibacterial surface coatings topographical architecture that can be applied that reduces the risk of infection. In this regard, the paper introduces the emerging research on antibacterial constructs highlighting the challenges and opportunities. In doing so, antibacterial biomaterials the offer the highest potential for reducing orthopaedic infections while combating AMR are discussed.

Keywords: antibacterial biomaterials; bactericidal topography; bacteria-repellent surfaces; antimicrobial resistance; implant infection.

1. Introduction

Developments in orthopaedic medical devices have made significant contributions to advancing medicine and improving patient lives [1–3]. When it comes to orthopaedic implants, their role is primarily targeted at restoring joints that undergo static and dynamic loading and are subject to wear [4–6]. These include devices that partially or fully replace hip, knee, ankle, shoulder, elbow, etc. Besides, they include fixation devices such as wires, pins, plates, and screws necessary to support implant fixation and loading [7–9].

In most cases, materials used for the fabrication of orthopaedic devices include titanium alloys (Ti6Al4V), cobalt-chromium alloys (CoCrMo), stainless steel, various polymers (PMMA and UHMWPE) and ceramics (alumina, zirconia, and hydroxyapatite) [10–14]. The introduction of an implant into the body is always associated with the risk of microbial infection, both from the foreign body and the surgical site. Consequently, orthopaedic implant infection is challenging that leads to major complications, revisions, amputations, and even death.

In most cases, orthopaedic implant infection is the result of implant surface bacteria that subsequently lead to biofilm formation leading to chronic infection. These infections feature bacteria that often fall within antimicrobial-resistant (AMR) strain which makes them difficult to eliminate post-biofilm formation using conventional antibacterial therapies. According to Tripathy *et al.* [15], in general, AMR claims at least 700,000 lives each year climbing to 10 million by 2050 as shown in Fig. 1. Bacterial infection results in orthopaedic implant failure either immediately as a result of non-healing or after years of implantation [16]. Some of the most implant infection causing microbes *S. aureus*, *S. epidermidis* and *E. coli* [17–19].

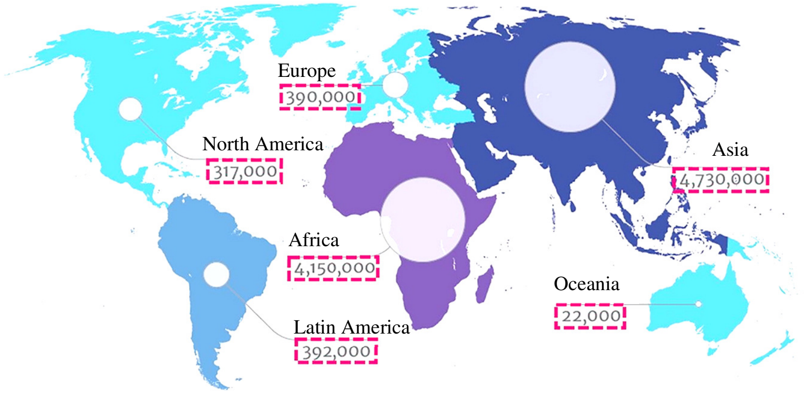

Fig. 1. Global distribution of deaths due to antimicrobial resistance by 2050 [15,20].

Developing antibacterial biomaterials that can induce infection resistance on implant surfaces is an option that offers a significant clinical advantage. Such a strategy can drastically reduce the initial risk of bacterial infection and prevent infection during the surgical procedure and the osteointegration period. It is also an opportunity to incorporate strategies that go beyond the current methods where the effectiveness is significantly affected by antimicrobial resistance [21–23].

Accordingly, the research community is active in identifying and developing numerous strategies to reduce or to eliminate the extent of bacterial attachment and biofilm formation on implant surfaces. The efforts are targeted at conceiving new biomaterial with the inherent antibacterial performance or on improving the performance of biomaterial surfaces through the bactericidal or bacteria-repellent coating. Techniques such as nanostructured topographies that induce bactericidal effects through cell wall rupture are also being experimented with and offer significant potential as an alternative to chemically active surfaces [24–26]. This paper is intended to introduce various emerging antibacterial techniques that can be adopted to reduce orthopaedic implant infection. In doing so, an attempt is also made to highlight strategies that offer the highest potential by going beyond the current challenges associated with antimicrobial resistance and cytotoxicity.

2. Bacterial infection of orthopaedic implants

Despite the many advances in biomaterials used for the fabrication of orthopaedic implants, a significant proportion of these devices result in implant-related bacterial infections [27–29]. As shown in Table 1, a significant proportion of these infections are caused by *S. aureus* and *S. epidermidis* [30] with a large prevalence of antimicrobial resistance. *Staphylococci* are Gram-positive, non-spore forming facultative anaerobes that grow by aerobic respiration or fermentation featuring diameters of 0.5 to 1.5 µm. They are characterised by individual cocci, which divide in more than one plane to form grape-like clusters [31].

The rate of infections is worsened by the emergence of antimicrobial-resistant bacterial which has also become prevalent accelerated by the spreading as demonstrated in Fig. 2. The economic and social costs of orthopaedic implant-related infections make the situation all the worse [32–35]. Generally, direct hospital costs, related to the treatment of periprosthetic joint infections, range from approximately £21,937 in the UK to $30,300 in the US with the long-term economic effect coming at approximately $390,000/case based on the Markov utility model [33,36–39].

Numerous strategies have been investigated over the last few years to prevent bacterial adhesion and subsequent biofilm formation on biomaterials. In most cases, the approach is related to modifying the biomaterial surface either chemically or topologically to result in bacteria-repelling (ante-adhesive) or killing (bactericidal) surfaces [40–42]. In the following section of the paper, the mechanism of action of these antibacterial surfaces are presented and potential aspects are highlighted.

Table 1. Prevalence of Staphylococci and antimicrobial resistance in orthopaedic implant infections compiled from respective studies reporting representative small samples [17].

Infection	Microorganism	Antimicrobial resistances	Ref.

Prostheses (various)	*Staphylococci*	Penicillin, ampicillin, clindamycin, erythromycin, gentamicin, tobramycin, and vancomycin.	[43]
Knee (periprosthetic joint infections)	*Escherichia coli* *Klebsiella Pneumoniae*	Ciprofloxacin, gentamicin, ciprofloxacin, gentamicin.	[44]
Hip and knee arthroplasties	*Coagulase-negative Staphylococci* *S. aureus*	Cefazolin, methicillin, cefazolin.	[45]
Aseptic loosening	*Staphylococci* *Coagulase-negative Staphylococci* *S. epidermidis* *S. warneri*	Methicillin, macrolides, lincosamides, streptogramins, aminoglycosides, cotrimoxazole, ciprofloxacin, fusidic acid, and rifampin.	[46]
Revision for periprosthetic joint infections	*S. aureus* *Coagulase-negative Staphylococci*	Tomethicillin and gentamicin	[47]

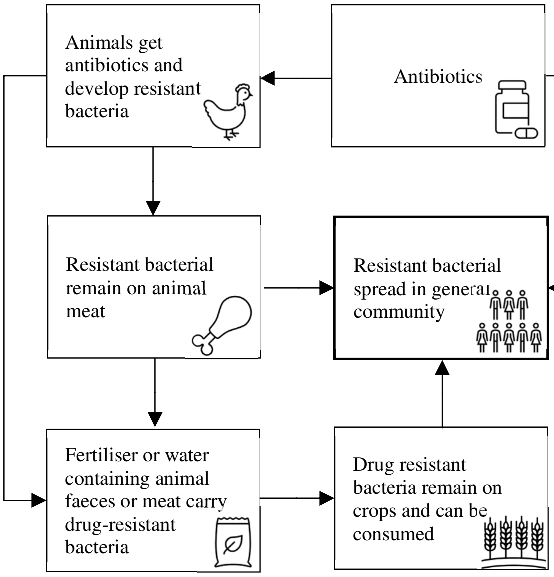

Fig. 2. Spreading of antimicrobial-resistant bacteria in the community, modified from [48].

3. Antibacterial biomaterials

3.1. Qualifiers for antibacterial biomaterials for orthopaedic application

A wide range of materials and surface enhancement techniques are being investigated by researchers for their antibacterial efficacy [49]. However, for these materials to be used as a biomaterial for orthopaedic application, simply being antibacterial is not enough [50–52]. In this regard, material or surface being antibacterial does not quality it to be an antibacterial biomaterial. To qualify as an antibacterial biomaterial that offers potential for infection resistance, the following qualifiers must be considered in the order presented.

i. Biocompatibility: an acceptable material functionality without any unwarranted reaction at the tissue level or to the immune systems [53–55]. The extent to which biocompatibility is required depends on the biomedical device classification as discussed by Arjunan *et al.* in [4]. Generally, acceptable evaluation is carried out regarding cytotoxicity, carcinogenicity, mutagenicity, pyrogenicity, allergenicity, and thrombogenicity.

ii. Mechanical behaviour and interface stability: the antibacterial material, coating, or surface should feature the necessary mechanical performance and stability to sustain load-bearing and osseointegration [56–58]. Generally, these properties fall within the mechanics of materials and include a range of properties the characterises stiffness, strength, hardness, toughness, and durability to name a few.

iii. Antibacterial efficacy without adverse cytotoxicity: the material should feature adequate antibacterial performance that offers infection resistance that is demonstrated *in vitro*, *in vivo,* and in an appropriate model suitable for orthopaedic surgical site infections (SSI) periprosthetic joint infection (PJI) [59–61]. The adequate cytotoxicity aspect is significant as the material should not interact adversely with generation and implant reintegration which is required in almost all orthopaedic cases.

iv. Sustained-release during the duration of the "risk period": while there is no official recommendation regarding how long the antibacterial effectiveness should last. A reasonable estimation should be the duration of the risk of infection which largely depends on the type of implantation and the tissue engineering construct [62]. Long term effectiveness is recommended for the case of prosthetic joint infection [63].

3.2. Factors influencing the antibacterial performance of a biomaterial

Several methods from basic research have been translated to induce antibacterial performance in orthopaedic implants [29,64,65]. The techniques include anti-adhesive properties, antimicrobial surfaces, drug eluding bactericidal coating, serums, and material morphology as shown in Fig. 3. In addition to the direct antibacterial properties, numerous factors dictate bacterial adherence to biomaterials surfaces including surface characteristics such as roughness and hydrophilicity [66–68].

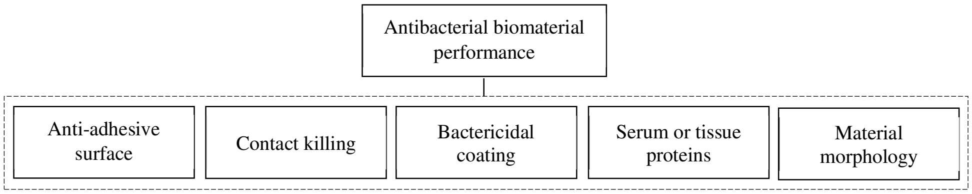

Fig. 3. Factors influencing the bacterial-biomaterial interaction in orthopaedic implants.

3.2.1. Material morphology

Other than for specific nano-structured architecture, surface roughness, in general, is favourable for bacterial adhesion [69–72]. According to Orapiriyakul *et al.* [66] when compared to flat surfaces, bacterial thrive in rough surfaces due to the increased surface area resulting in an enhanced binding ability. Studies conducted by Scheuerman *et al.* [73] confirm this by coating a rough substrate with polymer resulting in reduced biofilm formation. This is because such coating levels out the micro size peaks and valleys causing a smooth surface. In most cases, the resulting reduced valleys in the surface become comparatively smaller making it unsuitable for bacterial adhesion resulting in reduced binding [74].

3.2.2. Serum or tissue proteins

According to reviews carried out by Katsikogianni *et al.* [75] and An *et al.* [75] serum and tissue proteins such as fibronectin (FN), fibrinogen (FG), and albumin can influence antibacterial behaviour. Fibronectin (FN) mediates a wide variety of cellular interactions with the extracellular matrix (ECM) and plays important roles in cell adhesion, migration, growth, and differentiation [76]. FN plays various roles including adhesive interactions between cell wall, wound healing, haemostasis, and tissue repair. FG on the other hand is a key player in blood coagulation, platelet adhesion, and haemostatic processes [77,78].

3.3. Bactericidal biomaterials

Antibacterial biomaterials can be classified based on the mechanism by which they inhibit bacteria as shown in Fig. 4. Consequently, bactericidal biomaterials are surfaces or surface treatments where the basic mechanism is to kill the bacteria either through surface contact, ion leaching, or drug elution. Some examples of such material in the form of coating applied to orthopaedic implants are listed in Table 2. Although before employing orthopaedic implants the biocompatibility must be accessed based on the application and length of implantation [79,80].

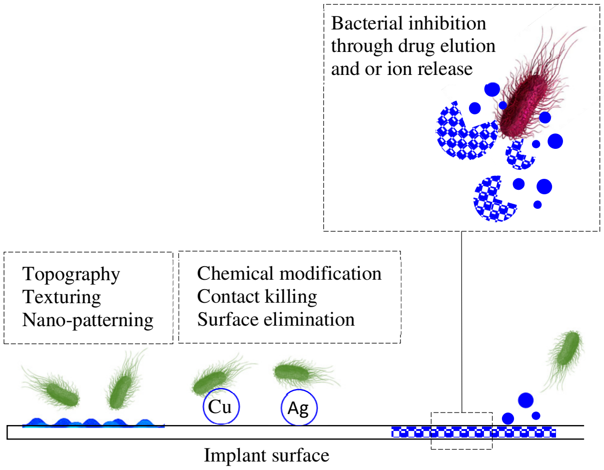

Fig. 4. Types of bactericidal antibacterial approaches to biomaterial surfaces for orthopaedic application.

Bactericidal biomaterials can include metallic surfaces (Ag, Zn, Cu, Zr) [81–83] or non-metal elements (Se, hydrogels) [84], organic substances (antibiotics, antibacterial peptides, chitosan) [85,86], amongst others. Bactericidal biomaterials inhibit microbes not only based on material chemistry, but another class of surfaces falls within this category but uses topographical features such as nanostructured needles also to kill bacteria. A brief introduction on to the various class of antibacterial biomaterials that comes under the broad classification of bactericidal biomaterials is presented in the subsequent section.

Table 2. Some examples of bactericidal biomaterials from the literature that has shown effectiveness against the common infection-causing bacteria *Staphylococcus aureus* in orthopaedic implants.

Type	Coating	Substrate	Bacteria	Ref.
Bactericidal	Silver	Titanium, silver	*Staphylococcus aureus*	[87–90]
	Copper	Stainless steel, titanium		[65,83,91,92]
	Zinc	Glass		[93]
	Iodine	Titanium		[94,95]
	Chitosan-vancomycin	Titanium		[96]

3.3.1. Antibacterial metallic biomaterials

Metallic surfaces and nanoparticles based on silver (Ag), copper (Cu), zinc (Zn), gold (Au), nickel (Ni), palladium (Pd), selenium (Se) along with nanoscale zero-valent iron and ferrite have shown significant antibacterial performance [24,48,91,97–100]. Among these metals, although they have shown some effectiveness in the bulk form, their performance is often related to ionic release and are often highly effective as nanoparticles. The advantage with metallic components over other antimicrobial biomaterials is their complimentary mechanical performance [101–105] and ease of processing through well-established techniques. However, long term cytotoxic and biocompatibility data for some of these materials are still not available and hence are yet to be adapted for routine orthopaedic applications.

Out of all the suitable metallic candidates, the proliferation of research is happening on Ag followed by Cu and Zn for orthopaedic application. Ag when exposed to a bacterial environment becomes biochemically active and interfere with bacterial cell membrane permeability. As shown in Fig. 5 Ag has also been shown suitable for additive manufacturing which offers significant potential for its application for patient-specific implants and other medical devices as demonstrated in [87,106–109]. Studies conducted by Fielding *et al.* [110] and Noda *et al.* [111] also shows that Ag surface coatings can be developed with significantly reduced cytotoxicity making them suitable for long-term implantation.

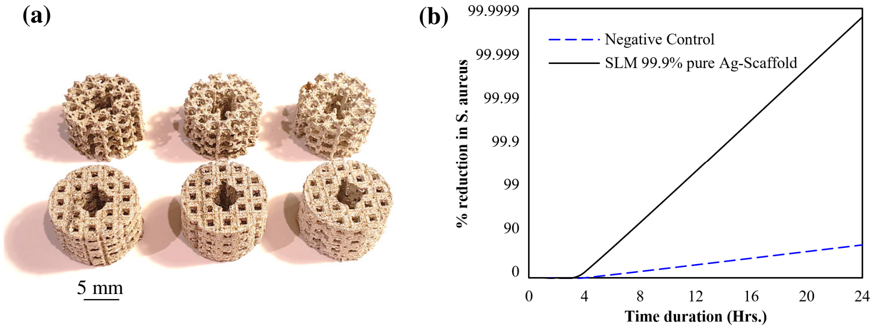

Fig. 5. Additively manufactured antibacterial silver scaffold showing (a) prototypes as printed and (b) resulting in antibacterial performance.

Cu and Zn other metallic components that show antibacterial potency for a variety of bacterium [112–116]. Cu have shown [117] to exhibit antimicrobial activity against *Micrococcus luteus*, *S. aureus*, *E. coli*, *K. pneumoniae* and *P. aeruginosa* in addition to Methicillin-resistant *Staphylococcus aureus* (MRSA). According to Makvandi *et al.* [48], the overall antibacterial outcome when using Cu is comparable to Ag and certain antibiotics. The antibacterial activity of Cu is primarily a result of copper ion release that subsequently bind with the bacteria's Deoxyribonucleic acid (DNA) [92].

3.3.2. Organic antibacterial biomaterials

Chitosan is a biosynthetic polysaccharide that is the deacylated derivative of chitin. Chitin is a naturally occurring polysaccharide that can be extracted from crustacean exoskeletons or generated via fungal fermentation processes. According to Gallo et al. [118], although the mechanism is not fully understood, Chitosan has antibacterial properties [119]. In particular, studies conducted by Tan *et al.* [120] refer to quaternized-chitosan, a derivative that features significant antibacterial efficacy against a range of bacterial strains. When it comes to the application of these materials into orthopaedic implants, they are more likely to be formulated as bifunctional coatings to titanium or cobalt-chromium substrates. Other synthetic candidates that offer antibacterial properties include quaternary ammonium compounds (QACs), antibacterial enzymes, and antibacterial peptides. According to Olmo *et al.* [121] quaternary ammonium compounds are charged molecules capable of causing charge imbalance in a suitable environment, resulting in disruption of the bacterial cell membrane to initiate antibacterial performance.

3.3.3. Bactericidal topography

The use of physical nano-topography to kill bacteria without the need for chemical derivatives or targeted antibiotics is a rapidly evolving area of research [122]. Bactericidal topography should not be confused with low-adhesive or superhydrophobic surfaces [67]. The topography discussed in this section allows bacterial attachment which subsequently will be eliminated through a complex killing action primarily involving cell wall rupture. A good example of such topography from nature is the Cicada (*Psaltoda claripennis*) wing surface that has demonstrated bactericidal effects as shown in Fig. 6.

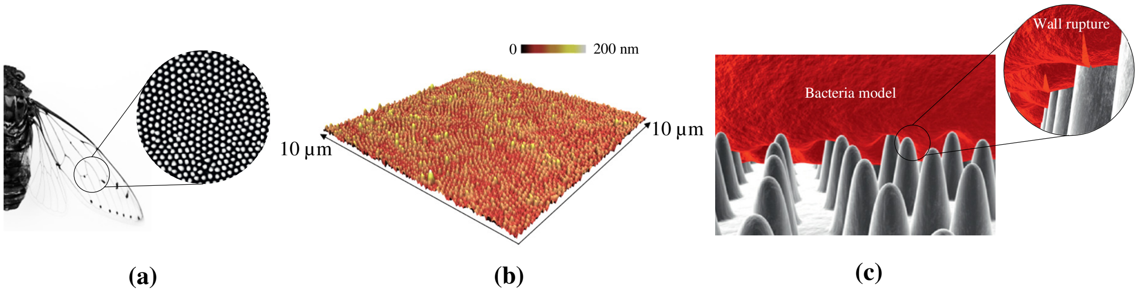

Fig. 6. Illustrated example of the bactericidal topography of Cicada wing architecture, where (a) shows the macroscopic and microscopic topography adapted from [123], (b) shows the 3D representation of the surface architecture and indicative dimensions [123], and (c) shows the cellular attachment onto the Cicada wing surface topography and the subsequent cell wall rupture adapted from [67].

Studies have shown that mimicking such topography can result in significant bactericidal effects where the performance is dictated by the nano-topography as oppose to surface chemical effects [124–127]. It is important to note that these topographic architectures are not antibiofouling as they allow cell attachment, however, the attached cells are subsequently killed because of mechanical ruptured within a short period.

Overall, a wide range of nano-topographies has shown to be antibacterial with dimensional ranges as shown in Fig. 7. The most common types of antibacterial topographies studied were pillars, wires, and spike-like structures at the nanoscale with results as summarised in Table 3. So far, microfabrication techniques such as reactive ion etching, hydrothermal treatment, and nano-imprint lithography seem to be explored for the fabrication of experimental topographies. The material being studied include silicon, titanium, zinc, and gold amongst others [128–133]. Overall, the use of topographical architecture at the nanoscale to induce antibacterial properties seems to be a highly promising direction. While the fabrication and optimisation of nano-topographic architectures remain a challenge, the physical bactericidal effect prevent s the development of antibacterial resistance often observed under repeated chemical exposure [134–138].

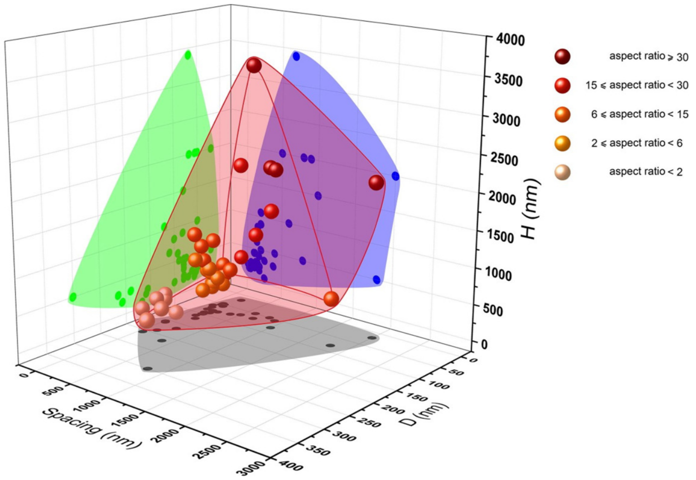

Fig. 7. Effective dimensions for bactericidal nanopatterns as brought together by Modaresifar *et al.* [122]. The area highlighted in red can be attributed to the topographical dimensional range that results in bactericidal effects. A significant proportion of all bactericidal topographies in literature feature a height, diameter, and spacing of 100-500 nm, 10-300 nm, and 10-380 nm, respectively.

Table 3. Examples of nanoscale topographies that have shown bactericidal antibacterial effects [139].

Type	Nano-topography	Manufacturing	Material	Bacteria	Ref.
Bactericidal	Pillars	Reactive-ion beam etching	Si	*Pseudomonas aeruginosa*	[140]
	Wire brush type array	Alkaline hydrothermal	TiO_2		[133]
	Bio-inspired micro-nano (dragonfly wings)	Hydrothermal etching	Ti		[141]

3.4. Bacteria-repellent biomaterials

When it comes to characterising an antibacterial biomaterial, any surface that prevents biofilm formation is a suitable candidate [142–145]. As such this could involve, materials and strategies that prevent bacterial adhesion as oppose to inducing a bactericidal effect. In this regard, hydrophilic, hydrophobic, and charged surfaces cannot be discounted when discussing antibacterial biomaterials. These materials are generally categorised as bacteria-repellent, anti-adhesive, or antibiofouling materials. However, when considering these materials for orthopaedic implants involving tissue reintegration, critical evaluation of host cell attachment is required.

Table 4. Examples of bacteria-repellent (anti-adhesion) antibacterial biomaterials that are chemically and topographically derived.

Type	Repellent-surface	Manufacturing	Base material	Bacteria	Ref.

Surface coating	Silicon ions	Ion implanter and sputtering	316 stainless steel	*Staphylococcus aureus* and *Staphylococcus epidermidis*	[146]
	Selenium	Dried under laminar flow	Titanium alloy		[147]
	Polymer	Spin-coating	Glass		[148]
Surface topography	Bioinspired (Lotus leaf)	Femtosecond laser ablation	Titanium	*Staphylococcus aureus* and *Staphylococcus epidermidis*	[149]
	Lamella-like	Direct laser interference patterning	Polystyrene	*Staphylococcus aureus*	[150]
	Bioinspired (Shark skin)	Cast embossed	Polydimethylsiloxane elastomer, acrylic films	*Staphylococcus aureus* (MSSA, MRSA)	[151]

In most cases, cell attachment will be challenged at the anti-adhesive interface resulting in a poor implant-tissue interface. Consequently, bacterial repellent biomaterials are most suitable for the development of non-fixation complimentary implant structures such as plates, screws, or intramedullary nails where antibacterial performance is required without the need for tissue integration [152–155]. Bacteria-repellent materials can be generally classified into those that induce these effects as a result of material chemistry (surface coating) or surface topography (nano-micro architecture). Some examples of such materials and the resulting performance from literature are summarised in Table 4.

4. Future perspective

According to Public Health England (PHE)[156], there were an estimated 61,000 antibiotic-resistant infections in England during 2018, a 9% rise from 2017. According to US estimates [48], there are ~2 million infections and ~23,000 deaths yearly as a result of antibiotic-resistance. The primary pathogens include *Entercoccus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species* [157]. As a result, new antibacterial methodologies for fighting infections are required. As discussed thus far, the research in this domain is highly active with numerous materials and methods being tested to improve orthopaedic implant functionality.

Depending on the functionality required, antibacterial biomaterials can be selected to either repel bacteria by preventing attachment or inactivate them through various approaches. Although chemically-based bactericidal mechanisms seem to be effective and can be fabricated efficiently, the duration of release (antibacterial effect) and cytotoxicity remains key questions that are yet to be answered. When it comes to adopting anti-adhesive surfaces for orthopaedic implants, concerns are often raised regarding cell attachment requirements associated with tissue reintegration. Consequently, long terms studies on combined tissue reintegration and antibacterial effects required to be studied. Based on the data available, it may be that anti-adhesive surfaces are best suited for non-fixation orthopaedic structures.

The latest advances in bactericidal biomaterials that can mechanically eliminate (kill) bacteria using surface topography offers significant potential. The fact that physical cues such as roughness, stiffness, and shape features at the sub-micron and nanoscale can be manipulated for bacterial cell wall rupture go beyond the current limitations associated with cytotoxicity and chemical surfaces leading to antimicrobial resistance (AMR). Furthermore, studies have shown that repeated exposure to chemically based bactericidal biomaterials, for example, Ag nanoparticles result in certain bacterial strains developing AMR [134]. Although controversy exists over the exact killing mechanism, topography based bactericidal biomaterials can be a good starting point in the design of antibacterial biomaterials for future orthopaedic implants and tissue engineering constructs. However, the interaction of topographic surfaces to tissue reintegration and biocompatibility are areas requiring further investigation.

5. Conclusion

The year-on-year rise in antimicrobial resistance calls for improved techniques relating to the treatment and prevention of orthopaedic implant infections. Despite numerous efforts, implant infection is still a challenging problem that requires replacement of both the infected device and tissue. Therefore, appropriate strategies where antibacterial performance can be an inherent part of orthopaedic devices is highly advantageous to reduce human cost and antimicrobial resistance. Accordingly, the paper systematically evaluates the emerging approaches regarding the development of bactericidal chemical surfaces, bacteria-repellent, and bactericidal topographies to identify suitable directions in functional antibacterial biomaterials. The recent developments in bactericidal topography offer significant insights regarding the development of functional antibacterial biomaterials for orthopaedic application. However, the process of bacterial adhesion and proliferation is highly complex which requires future research to offer a better understanding. Data is also needed regarding the biocompatibility, cytotoxicity, and combined effect of osteointegration and antibacterial performance in a clinical setting for such constructs. Overall, further research in the field will bring functional antibacterial biomaterials for orthopaedic application that goes beyond the current challenges associated with antimicrobial resistance.

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