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Antibacterial bioactive materials

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Abstract: Bioactive materials with antibacterial properties have significant medical interest. Antibacterial bioactive materials can be prepared by simple combination of antibacterial substances with materials such as hydrogels, ceramics, metals, and polymers, in different forms, such as fibres, foams, films or gels. The delivery of the antibacterial molecules will lead to the killing of bacteria. Another approach is to design the material itself to possess the antibacterial properties, especially at the surface of the material. The applications have been found in orthopaedics and cardiovascular grafts, as a means of reducing the incidence of infection. In the wound care industry, using antibacterial bioactive materials to control infection is always the first line for wound treatment. However, there are still considerable limitations, including the difficulty in treatment of the infection at depth, the control of the biofilm formation, and the development of generic and specific antibacterial bioactive materials. In future, bioactive materials based on biomimetic materials with antibacterial properties will be developed from natural resources to minimize the negative impact on the human body.

Key words: antibacterial materials, anti-infection materials, biofilm, wound care.

5.1 Introduction

Antibacterial medicine has been commonly used for the treatment of infections. The definition of an antibacterial bioactive material is a material possessing the activity to destroy bacteria or suppress their growth or their ability to reproduce. Over the past several years, infectious disease management has become an increasing challenge for physicians. Management of bacterial infection has become difficult due to the emergence of drug-resistant bacteria. There has been an alarming increase in the number of resistant Gram-positive organisms over the last 5 years.

These Gram-positive organisms include: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Streptococcus pneumoniae*. Reports from several centralized agencies that follow bacterial resistance trends indicate that the prevalence of methicillin-resistant *S. aureus* (MRSA) has increased from 25 to 37% and vancomycin-resistant *E. faecium* (VRE) from 35 to 65% in the last 3 years alone. These resistant organisms represent a major cause of morbidity and mortality in hospitalized patients with hospital-acquired infections (HAIs). However, the problem of resistant Gram-positive organisms is not limited to the hospitalized patient. Outpatients have also been affected, with the emergence of penicillin-resistant *S. pneumoniae* (PRSP), a cause of community-acquired pneumonia [1].

Hospital-acquired infections and the healthcare environment have attracted considerable worldwide attention in the past few years, owing to many occurrences and outbreaks of MRSA and VRE caused morbidity and mortality. The search for methodologies to prevent and treat infections is currently an important clinical topic.

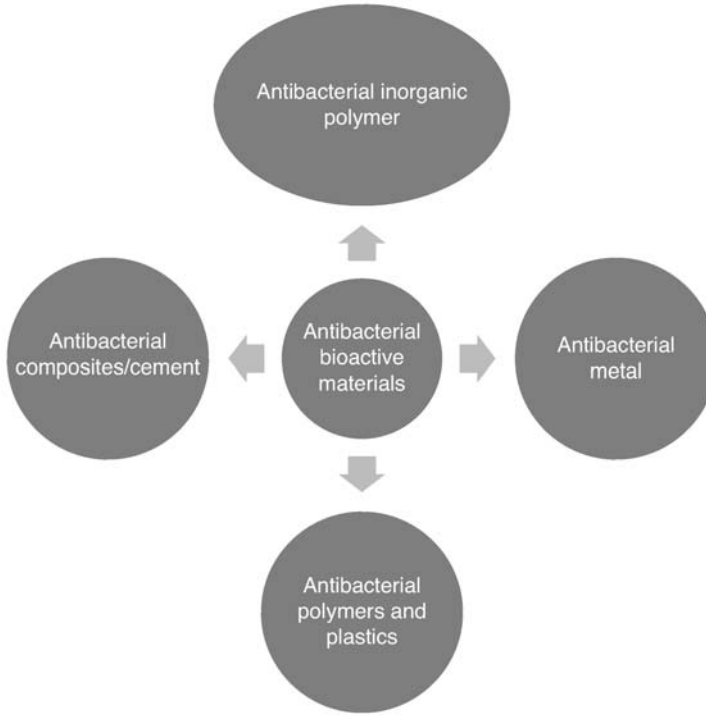
It has been estimated that the current global anti-infective market is valued at US$66.5 billion, with bioactive antibacterial agents accounting for over 50% of sales. The antibacterial market is set to grow to over US$45.0 billion by 2012, driven by the uptake of newer antibacterial agents, such as glycopeptides and carbapenems, which demonstrate resistance to MRSA and VRE, as well as other emerging strains. Pharmaceutical companies continue to develop a new generation of antibacterial agents, such as cephalosporins, macrolides, and quinolones, to overcome the major issue of drug resistance. In addition, a number of new drug classes, effective in multi-drug-resistant organisms, such as dihydrofolate reductase inhibitors (DHFRs), are under evaluation [2].

In this chapter, the focus is on bioactive materials with antibacterial functionality for use in the medical device related health care industry, for example, wound care [3], dental and orthopaedics [4, 5], and cardiovascular. The antibacterial materials discussed in this chapter include: antibacterial inorganic polymers, such as bioglass, ceramics, glass–ceramics, and zeolites; antibacterial composites, such as bone cement; antibacterial metal; antibacterial polymers and plastics (Fig. 5.1).

5.2 Antibacterial materials

5.2.1 Antibacterial inorganic polymer

Antibacterial ceramics have recently received great attention, because of their wide range of applications, including electronics and medical applications, and various forms, such as fibres, fabrics, building materials,



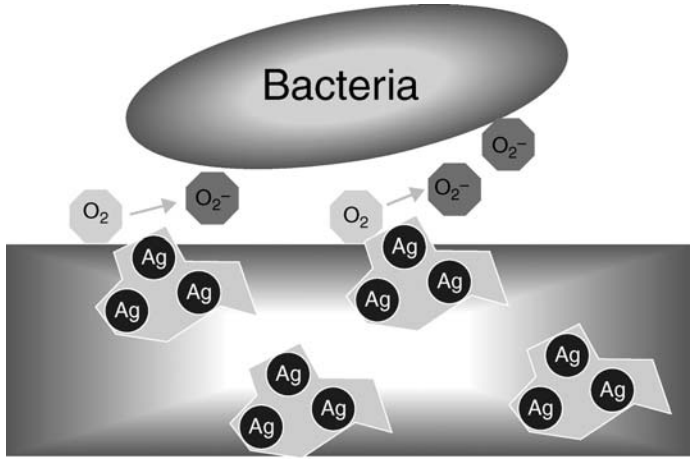
5.1 The classification of antibacterial bioactive materials.

storage containers, and devices. With or without the incorporation of certain metal ions into the ceramics, bioceramics, including bioglass, ceramics or glass–ceramics, can exhibit excellent antibacterial properties [6–8].

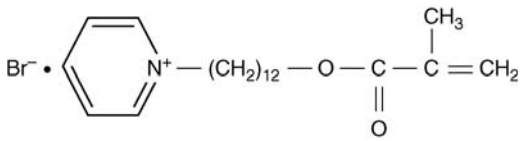
Among the metallic elements, heavy metals such as silver, zinc, copper, mercury, tin, lead, bismuth, cadmium, chromium, and thallium possess antibacterial properties and the exchange with these metals imparts antibacterial activity to inorganic polymers, such as zeolites and zirconium [9–12]. The antibacterial effects of silver-supported zirconium phosphate or silica gel are not due to the release of silver ion but to the activation of oxygen based on the catalytic action of silver [12, 13] (see Fig. 5.2).

5.2.2 Antibacterial composites – bone cement

It is a common practice to incorporate antibacterial materials into curable resins to obtain antibacterial composites for medical application. For example, loading polymethylmethacrylate (PMMA) bone cement with antibiotics to reduce infection rates has been proposed [14, 15]. Antimicrobials, such as chlorhexidine, have been incorporated into both



5.2 Schematic diagram of the antibacterial effects of composites containing non-releasing silver-supported powders. Activated oxygen is produced based on the catalytic action of silver in composites to show antibacterial effects [12].



5.3 Chemical structure of 12-methacryloyloxydodecylpyridinium bromide (MDPB).

glass ionomer cements (GICs) and resin-modified glass ionomer cements (RMGICs) to improve their antibacterial properties. This agent has been described as the gold standard for antibacterial application [16].

Other than the above approach of direct incorporation of antibacterial medicine into a bone cement system, a monomer such as 12-methacryloyloxydodecylpyridinium bromide (MDPB) (see Fig. 5.3) has the potential to be polymerized and incorporated into dental resin-based materials, such as dentin bonding primer/resin, to make a composite with bactericidal activity but having no adverse effect on biocompatibility [17, 18].

Composites based on biodegradable polymers and ceramics or bioglass have found wide application in bone tissue repair. The inclusion of antibacterial properties to combat bone tissue infection is an attractive approach in clinical application. The design of the bioactive materials can be achieved by simple blending and mixing of antibacterial materials or antibacterial molecules into the bulk to achieve a controlled release of the antibacterial substance. However, as the surface is normally the place where

there is contact with the body, a surface with anti-infection function is sometimes critical. Tokuda *et al.* [19] developed a method of blending PLA and calcium carbonate and siloxane with the mercapto groups to form a composite for guided bone regeneration. The mercapto groups have the capability to adsorb silver at the composite surface to ensure the antibacterial properties for the bone implant.

5.2.3 Antibacterial metal

Silver ions have long been recognized to possess strong inhibitory and bactericidal effects, as well as a broad spectrum of antimicrobial activities. Silver-doped titanium dioxide powder can show a marked antibacterial activity even without the presence of light. The antibacterial activity of the silver-doped titania material was influenced by the methods of preparation, such as sol–gel, ion-exchange, melting, and the effect of reactants (sulfate, chloride, and organic derivatives) and the calcination temperature [20].

Another method for producing antibacterial metal is to deposit noble metal at a surface of another material to form a thin film, using a process called reactive magnetron sputtering, which is a form of physical vapour deposition. For example, NUCRYST developed a technology to produce a nanosilver antibacterial thin metal surface. The process is reviewed as follows:

> in a vacuum chamber, pure silver is bombarded with positive ions to liberate or sputter individual atoms. The silver atoms are activated by an entity known as plasma, often referred to as a fourth state of matter. These silver atoms are then re-condensed to form new high-energy nanocrystalline structures on substrates – such as high-density polyethylene for non-adherent wound care dressings [21].

The nano-crystal silver used in NUCRYST Pharmaceuticals' existing medical devices and emerging pharmaceutical product line is between 1 and 100 nm and is being developed to target a wide range of potential pharmaceutical products [22–24].

Titanium dioxide (TiO_2) under ultraviolet A (UVA) has a well-recognized bactericidal effect on the treatment of bio-implant-related infections [25, 26]. Many commercial products have been developed based on this technology for antibacterial applications in hospital and other bacteria-prone environments.

Metals such as copper (Cu) and silver (Ag) have been deposited photocatalytically on TiO_2 coatings for the purpose of enhancing their antibacterial activity and to make these coatings work even in the dark. For example, antibacterial tiles based on this technology work effectively both under dark and illumination conditions, the effect being much higher under

light. This can be extended to fabricate photocatalytically modified Ag–TiO_2 coatings on silicone catheters and medical tubing, which effectively sterilize the microorganisms under dark conditions. Such coatings are useful for indwelling catheters, which are used inside the body, where guiding of light is a problem.

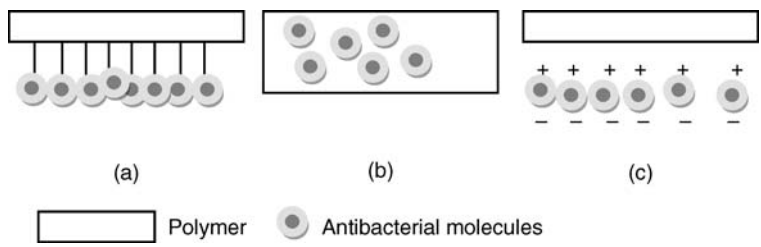
5.2.4 Antibacterial polymers

To design an antibacterial polymer, there are three approaches to have the antibacterial molecules incorporated into the system: covalent bonding, physical mixing, and physical complexation (Fig. 5.4).

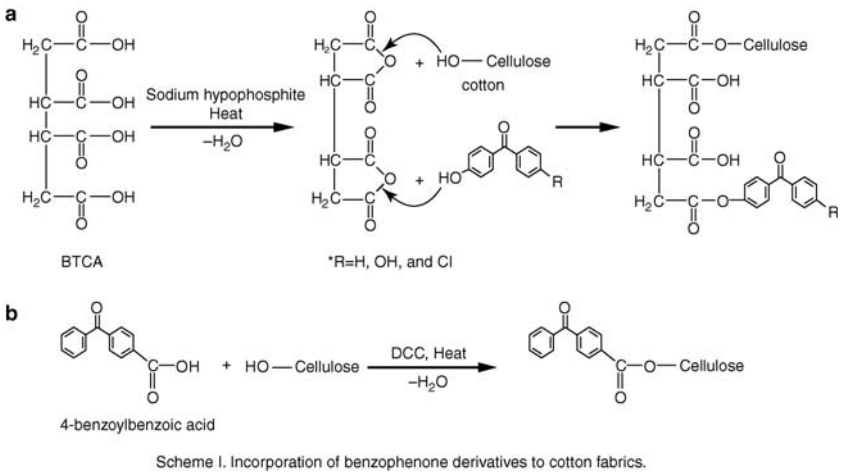
Covalent bonding

This is an approach to permanently attach the antibacterial moieties to the polymer system via covalent bonds. For example, antibacterial moieties, such as different benzophenone chromophoric groups, were incorporated onto cotton fabrics by reacting with 4-hydroxybenzophenone, 4, 4′-dihydroxybenzophenone, 4-chloro-4′-hydroxybenzophenone and 4-benzoyl-benzoic acid, and via a pad-dry-cure method. Antibacterial assessment of the benzophenone derivative-treated cotton fabrics was performed against *S. aureus* and *E. coli*. 4-Hydroxybenzophenone-treated cotton fabric demonstrated the most effective antibacterial ability, as shown in Fig. 5.5 [27].

Cellulose fabric can be chemically modified with the triazine derivatives containing the multi-cationic benzyl groups as shown in Fig. 5.6. The novel cellulose biomaterial containing the multi-cationic benzyl groups displayed excellent, durable antibacterial properties [28].

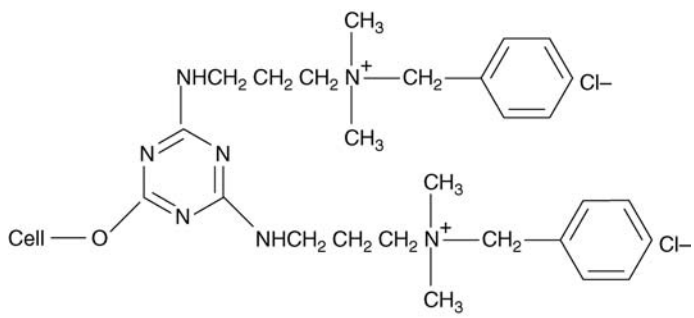


5.4 Design of antibacterial polymers: (a) covalent bonding antibacterial molecules on polymer surface; (b) polymer blending with antibacterial molecules; (c) complexing of antibacterial molecules with polymer via ionic or coordination.



Scheme I. Incorporation of benzophenone derivatives to cotton fabrics.

5.5 Covalent bonding antibacterial moieties on cotton fabrics.



Scheme 1. Chemical structure of the modified cellulose.

5.6 Covalent bonding antibacterial moieties onto cellulose.

Metal ion-containing polymers

Polymers having biocidal activities can be designed by introducing divalent transition metal salts metal ions, such as Zn^{++}, Cu^{++} into the polymer main chain to form a complete network [29–31]. These polymers have found application as antibacterial coatings [29] and they are soluble in dimethyl sulfoxide (DMSO), dimethyl acetamide (DMAc) and dimethyl formamide (DMF) [31]. In particular, poly(urethane–urea)s (PUUs) and poly (urethane–ether)s (PUEs) had satisfactory biocompatibility and biodegradability properties, which could potentially lead to a variety of blood-contacting applications. Other metal-containing polymers, utilizing sustainable resources, such as linseed oil-based polyesteramide, have also been developed for antibacterial purposes. It was found that minor incorporation

of zinc in linseed oil-based polyesteramide exhibited improved antibacterial activities against *E. coli* and *S. aureus* [32].

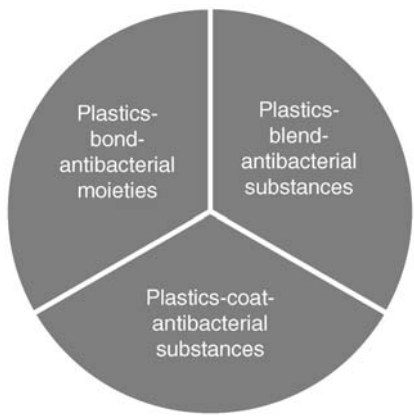
Antibacterial plastics

Plastics, combining low cost with good mechanical properties and easy processability, are widely used to prepare biomedical devices and food packaging, in which sometimes, antibacterial properties are essential. To obtain plastics with antibacterial properties, there are three general approaches, as shown in Fig. 5.7.

Water-insoluble antibacterial plastics via a chemical bonding approach is a type of environmentally friendly disinfection material, as it has no leaching of chemicals to the environment, and it has attracted much attention. For example, quaternary ammonium salts (QAS) moieties have been polymerized into plastics [33–36]. Organic–inorganic hybrid coatings containing QAS bonded to the organic–inorganic network were prepared from tetraethoxysilane and triethoxysilane terminated poly(ethylene glycol)-block-poly (ethylene) using a sol–gel process [37]. N-alkylated poly(4-vinyl-pyrdine) moieties [38, 39] have also been synthesized to demonstrate their effective long-term antibacterial properties.

Other than chemical bonding approaches, trials to achieve an antibacterial composite by simple blending can be carried out by two approaches.

1. Alterations to the resin components:
   (a) addition of soluble antimicrobial agents into the resin matrix [40–42];
   (b) immobilization of an antibacterial component into the resin matrix, utilizing an antibacterial monomer [43–45].



5.7 Approaches to the preparation of antibacterial plastics.

2 Alterations of the filler components:
   (a) addition of a component of silver as filler: silver-containing silica glass; silver zeolite/silver apatite; silver-supported zirconium phosphate/silver-supported silica gel [46–53];
   (b) addition of a non-biocide component as filler antimicrobial polymers and photocatalytic ingredients, which when exposed to light generate free radicals [42].

Antibacterial PVC composite

Polyvinyl chloride (PVC) is the most widely accepted biomaterial in medical applications. Microbial attack can be prevented by the incorporation of an effective biocide (also known as biostabilizer) into the plastic. There is a wide range of biocides available; this includes, among others: 10, 10′-oxybisphenoxarsine (OBPA), trichlorohydroxydiphenylether (Triclosan), n-octyl-isothiazolinone (OIT), 4,5-di-chloro-isothiazolinone (DCOIT), mercaptopyridine-n-oxide (pyrithione), butyl-benzisothiazolinone (butyl-BIT), metal-based biocides, such as organotin and silver, non-biocide additives, including inherently, antimicrobial polymers and photocatalytic ingredients, which when exposed to light generate free radicals.

To develop antibacterial PVC products, various types of antibacterial filler have been incorporated into the blending system to make composites for further processing into finished products. For example, zeolites containing Ag, Cu and zinc (Zn) powders have been incorporated into PVC blend to manufacture plastic products [52].

Other polymers such as thermoplastic olefins (TPO), thermoplastic elastomers (TPE), and polyurethanes, do not contain plasticizer, which can potentially provide a carbon source for microbial growth, but may still require protection from antimicrobials. Organic antimicrobial additives are compounded into the polymer, where they diffuse to the surface and destroy microorganisms by interfering with enzyme activity. As antimicrobial additive at the surface is used up or washed away, additive from the polymer matrix continues to come to the surface, providing extended performance [54, 55]. The strongest growth is for inorganic, silver-based biocides, with recent utilization in a broad range of polymers, applications and functions [53].

Antibacterial polymers have also been used as coating materials for the local delivery of antibiotics in implants. In general, they must be biocompatible and biodegradable, and the release profile of the active substance needs to meet the clinical requirements [56]. Commonly used coating materials are polyester urethane [57], polyester-polyurethanes containing different ratios of poly (lactic acid) diol and poly(caprolactone) diol [58], and other bioresorbable polymer, such as PLA and other coating materials [56].

5.2.5 Natural antibacterial materials

Researching alternative antibacterial materials to synthetic ones has been an attractive topic for many years. Natural antimicrobial peptides (AMPs) are the most popular natural biopolymers in terms of attention received. They can be cationic and anionic peptides. Typical examples are cecropins, defensins, thionins, amino-acid-enriched class, histone-derived compounds, beta-hairpin and lactoferrin, neuropeptide-derived molecules, aspartic-acid-rich molecules, aromatic dipeptides, and oxygen-binding proteins, such as bacteriocins [59].

Bacteriocins [60, 61] are usually non-toxic, odourless, colourless, and tasteless. Since their modes of action differ from those of conventional antibiotics, including their targeting of a much narrower range of bacterial species, cross-resistance of bacteriocins with systemically-administered antibiotics would be unlikely to develop. Also, because they are generally inactivated by one or more of the proteolytic enzymes present in the digestive tract of humans, they would be metabolized just like any other dietary protein. Finally, bacteriocins as natural products may have better public acceptance than synthetic chemical agents [59].

Lactoferrin (formerly known as lactotransferrin) is a glycoprotein, and a member of a transferrin family, which belongs to those proteins capable of binding and transferring $Fe^{3}+$ ions [62]. It was first isolated by Sorensen and Sorensen [63] from bovine milk in 1939. Lactoferrin affects the growth and proliferation of a variety of infectious agents, including both Gram-positive and negative bacteria, viruses, protozoa, or fungi [64].

5.2.6 Antibacterial nanomaterials

The rapid growth in nanotechnology has spurred significant interest in the medical application of nanomaterials. Many materials at the nanoscale exhibit superior antibacterial properties than their origins, which are not at the nanoscale. The most commonly reported antibacterial nanomaterials include: silver nanoparticles (nAg) [65–67], nanosilver-based nanocomposites [68–70], silver-liposome [71], chitosan-based nano-biopolymer [72], photocatalytic TiO_2 [73], fullerol [74], aqueous fullerene nanoparticles (nC60) [75], and carbon nanotubes (CNT) [76]. Among all the nanomaterials, nanosilver has been receiving the most attention.

Nair *et al.* [77] reported a one-pot synthesis of silver nanoparticle–polymer composites (Ag–PNCs) in water, involving the polycondensation of methoxybenzyl chloride (MeO-BzCl) directly on silver nanoparticle surfaces at room temperature, leading to highly soluble antimicrobial nanocomposites. The composites, which are soluble in a range of organic solvents, precipitate in the reaction vessel, making their separation simple. Solutions

of the composites can be cast directly on substrates or made into freestanding films. The material was found to be stable for nearly 2 years. A range of substrates have been shown to become antibacterial by direct coating application of this material. It was claimed that the simple one-pot approach of this type to produce organic-soluble antibacterial coatings could have wide implications.

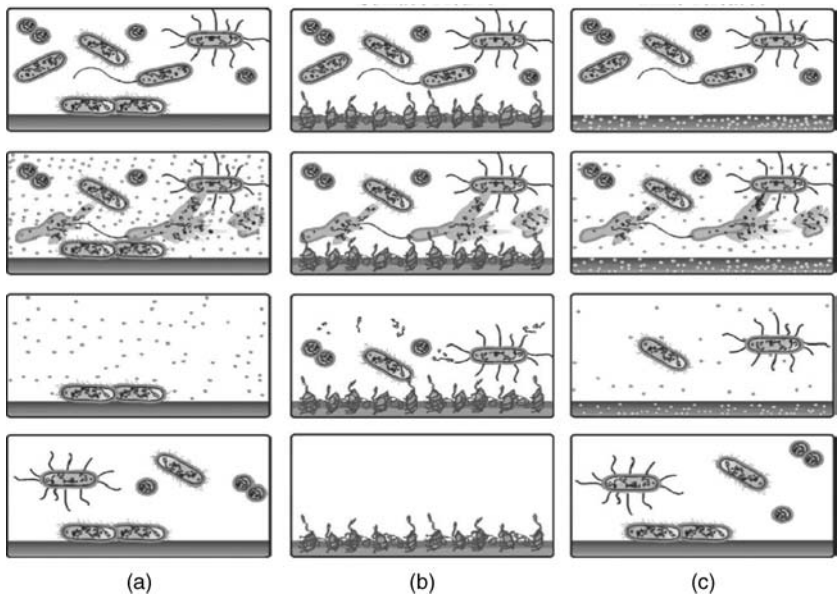
Barani *et al*. [71] reported a method for incorporating nanosilver particles into a liposome structure. The large silver-liposomes nanocomposites are transformed to the smaller silver-liposome nanocomposites (from 342 to 190 nm) through sonication treatment. The stabilized silver nanoparticles with various concentrations showed a good antibacterial activity against *Staphylococcus aureus*, a Gram-positive bacterium, and *Escherichia coli*, a Gram-negative bacterium.

Apart from liposome, silver (Ag) and silver sulfide (Ag_2S) nanoparticles can also be synthesized in a sago biopolymer, such as a starch matrix [68], hydrogel-based nanosilver nanomaterials [69], and other polysaccharide-based nanosilver systems, such as chitosan and alginate [70], where, at high concentrations, there is a release of silver nanoparticles from the composite in the water environment. In particular, for the hydrogel system, antimicrobial results show that these nanocomposite systems display a very effective bactericidal activity toward both Gram-positive and Gram-negative bacteria. However, the hydrogel does not show any cytotoxic effect towards three different eukaryotic cell lines. This is because the nanoparticles, immobilized in the gel matrix, can exert their antimicrobial activity by simple contact with the bacterial membrane, while they are not taken up and internalized by eukaryotic cells. This novel finding could contribute advantageously by responding to the growing concern over the toxicity of nanoparticles and facilitate the use of silver–biopolymer composites in the preparation of biomaterials.

5.3 Clinical applications of antibacterial materials

Despite the most stringent sterilization and aseptic procedures, bacterial infection remains a major impediment to the utility of medical implants, including catheters, artificial prosthetics, and subcutaneous sensors. Indwelling devices are responsible for over half of all nosocomial infections, with an estimate of one million cases per year (2004) in the USA alone. Device-associated infections are the result of bacterial adhesion and subsequent biofilm formation at the implantation site [78].

Much research has focused on developing a medical device surface that resists bacterial adhesion. In general, the mode of antimicrobial action of a surface may be (a) external, (b) surface active, and (c) time released (see Fig. 5.8). Each mode of action has its advantages and disadvantages. The



5.8 The three general modes of antimicrobial surface-mediated activity [79]: (a) external; (b) surface active; (c) time released.

external mode is represented by disinfectants as applied to surfaces that compromise the structural integrity of the microorganisms they contact. It is a blanket antimicrobial approach, where sufficient quantities kill the microorganism and may also affect humans. The surface-active mode can be represented by the selective transferral of antimicrobial surface agents into the microorganism until toxic accumulation occurs or membrane disruption occurs causing cellular leakage. Finally, the time-released mode consists of discharging antimicrobials in response to an environmental trigger, such as a change in surface pH, moisture, pressure induction, in which either of the latter conditions may be initiated by surface attachment of the antimicrobials, or a temperature change [79]. Most of the clinical applications of antibacterial materials are based on surface-active and time-release modes. However, in general practice, the first mode of disinfection is widely applied as a routine cleaning regime.

Typical applications of antibacterial materials range from products such as general hospital equipment (e.g. hospital beds and chairs), healthcare furnishings, medical packaging, and door handles, to high-grade medical devices like intravenous (IV) access systems, urological devices (catheters), bone cements, dental repairing materials, vascular grafts, and wound care products. These products with antibacterial properties can control the growth of bacteria on the surface of medical devices in an attempt to address the increasing problem of healthcare-acquired infections.

Table 5.1 Silver-based wound dressings

Product brand name	Manufacturers	Materials/structures	Modes of action
Acticoat	Smith & Nephew	Polyethylene mesh coated with nanocrystalline (<20 nm diameter) silver and two layers of rayon polyester	Sustainable release silver from nanocrystalline silver
Actisorb Silver 220	Johnson & Johnson	Activated charcoal dressing with bound silver	Adsorbing bacteria onto the charcoal component, where they are killed by silver
Aquacel-Ag hydrofibre	Convatec	70:30 sodium: silver carboxymethylcellulose hydrofibre	Sustainable release of silver ions
Arglaes	Maersk Medical UK/Medline	Silver/alginate	Sustainable release of silver ions
Contreet-H Contreet-F	Coloplast	Dense hydrocolloid /foam dressing bound with silver	Sustainable release of silver ions
SilvaSorb	Medline	Silver /hydrogel	Maintain a moist wound-healing environment with the benefits of sustained release antimicrobial silver
Silverlon	Argentum	Polymeric fabric coated with metallic silver	Sustainable release silver ions

5.3.1 Wound care

Wound care is a major healthcare market with an estimated value of US$10 billion in 2007, predicted to grow to US$12.5 billion in 2012 [3]. In this industry sector, the antibacterial materials play a very important role in combating wound infection. One development in the wound care market that has found favour with clinicians is the impregnation of products with an antimicrobial to reduce the risk of microbial infection.

The early use of silver in wound care was silver sulphadiazine (AgSD) cream, developed in the 1960s, for the treatment of burns [80]. Recently, a trend towards the use of wound cover dressings that contain silver has been evident [81], and today, a selection of foam, film, hydrocolloid, gauze, and dressings with silver technology – in which the wound dressings are impregnated with silver – are commercially available, as shown in Table 5.1.

Thomas and McCubbin [82, 83] compared the *in-vitro* effectiveness of various silver-containing products, using three methods – zone of inhibition, challenge testing, and microbial transmission testing – to demonstrate differences in the various dressings. Results against *Staphylococcus aureus*,

Escherichia coli, and *Candida albicans* suggested that polyethylene mesh had the most rapid antimicrobial effect due to its rapid release of silver. Hydrocolloid was similar but had a slower onset. Activated carbon had little activity on the surface, but organisms that were absorbed into the dressing were inactivated by the silver [82].

Iodine and polyhexamethylene biguanide (PHMB) are two popular antibacterial agents used in wound dressings. For example, company Smith & Nephew developed Cadexomer iodine (IodoflexAE and IodosorbAE), which is a three-dimensional starch lattice formed into spherical microspheres that trap iodine in the lattice. As fluid is absorbed, the pore size of the lattice increases, releasing iodine.

Polyhexamethylene biguanide (PHMB), also known as polyhexanide and polyaminopropyl biguanide, is a commonly used, fast-acting, and broad spectrum antimicrobial, providing activity against a wide range of bacteria (including MRSA, *Salmonella* spp., *Campylobacter* spp., *E. coli* 0157) and viruses (for example, VANTOCILTG antimicrobial has been independently shown to provide activity against FCoV, feline coronavirus at 0.2% product incorporation). PHMB-based wound dressing products include Kerlix AMD99, Excilon AMD99, and Telfa AMD99 (all from Tyco HealthCare Group, Mansfield, Massachusetts), XCellAE Cellulose Wound Dressing Antimicrobial (Xylos Corp, Langhorne, Pennsylvania) and COSMOCIL™ CQ antimicrobial (ARCH).

OXYZYME™ and IODOZYME™ active wound healing dressings are based on the biochemistry enzyme reaction system to generate a low level of hydrogen peroxide and iodine [84]. It has been claimed that the Oxyzyme dressing produces a peak surface concentration of iodine approximately 50 times lower than traditional 'iodine dump' dressings, such as those based on povidone-iodine. However, the concentration of the iodine is sufficient to produce an environment hostile to bacteria at the surface of the dressing.

5.3.2 Musculoskeletal and orthopaedics

Antibacterial materials have been widely used in dental and orthopaedic implants for many years, since bacteria are still a concern and a recurrent cause of failure for implants [85]. In the USA alone, the annual cost for the symptomatic treatment of dental infections in 1977 was estimated at over $11 billion , increasing to about $24 billion in 1984 and $34 billion in 1990 [4]. It was also reported that the infection rate of total joint arthroplasties is in the range 0.5–5% among over half a million implants used in the USA alone [86, 87]. The complication of infected implants quite often leads to surgical intervention at high health and social cost. For example, it was estimated that treatment of each single episode of infected arthroplasty costs over $50 000 [88]. Bone cements with antibiotics have been widely accepted

Table 5.2 Antibiotics-eluting bone cements [89]

Product brand name	Manufacturer	Materials/antibacterial substance	Clinical applications
Cobalt™ G-HV/ Palacos® G	Biomet	Gentamicin/PMMA bone cement	Arthroplasty
DePuy 1	Depuy	Gentamicin/PMMA bone cement	Arthroplasty
Cemex® Genta	Exactech	Gentamicin/bone cement	Fixation of prostheses to living bone for use in the second stage of a two-stage revision for total joint arthroplasty after the initial infection has been cleared
VersaBond™ AB	Smith & Nephew	Gentamicin/polymer powder and monomer liquid	Fixation of prostheses to living bone for use in the second stage of a two-stage revision for total joint arthroplasty after the initial infection has been cleared
Simplex® P	Stryker Orthopedics	Tobramycin / 75% methyl Methacrylate–styrene–copolymer/ 15% polymethyl-methacrylate/ 10% barium sulfate	Fixation of prostheses to living bone for use in the second stage of a two-stage revision for total joint arthroplasty after the initial infection has been cleared.

in clinical use, as shown in Table 5.2 [89]. Other than bone cements with antibiotics, coatings containing antibiotics in orthopaedics devices are also used clinically. For example, gentamicin, which has a relatively broad antibacterial spectrum, has been loaded on polymers for coating titanium implants [90, 91]. In addition, other antibiotics with broad antibacterial spectra, for instance, cephalothin, carbenicillin, amoxicillin, cefamandol, tobramycin, and vancomycin, have been used in coatings on bone implants [91–94].

5.3.3 Cardiovascular

Vascular graft infections represent one of the most challenging issues in surgery, having an incidence of 0.7–13%, with femoral site infections being the most common (13% incidence). Infection of vascular prosthetics implanted for arterial occlusive disease occurs in approximately 1–5% of patients, including early and late clinical presentation [95, 96]. Routine excision of infected peripheral arterial grafts and vascular reconstruction with extra-anatomic conduits are associated with mortality rates ranging from 10 to 30% and amputation rates of up to 70% [95]. Clinical data have

reported that in situ replacement with a rifampicin-bonded prosthesis has been accomplished successfully in a small number of patients and shows promising early results. Advances in the management of infected vascular prostheses over the last decade have led to improved mortality and decreased amputation rates with conventional excision and extraanatomical bypass. Newer methods, including in situ graft replacement with antibiotic-impregnated prosthetics, appear suitable for low-virulence *S. epidermidis* infection [96].

Stone *et al*. [97] implanted PMMA beads loaded with an antibiotic (vancomycin, daptomycin, or tobramycin/gentamicin, or a combination of these) to treat vascular surgical site (VSS) infections. Results indicate that antibiotic-loaded PMMA beads may be a useful adjunct in the contemporary surgical management of VSS infection involving a prosthetic graft. Another approach to treat methicillin-resistant *Staphylococcus aureus* (MRSA) or *S. epidermidis* prosthetic vascular graft infections has been carried out by in situ replacement with a rifampicin bonded Gelsoft graft [98].

An InterGard Silver (IGS) collagen and silver-acetate-coated polyester graft was used to replace an infected vascular prosthesis in situ. Preliminary results in this small series demonstrate favourable outcomes with IGS grafts used to treat infection in abdominal aortic grafts and aneurysms caused by organisms with low virulence. Larger series and longer follow-up will be required to compare the role of IGS grafts with other treatment options in infected fields [99]. A multicentre clinical study further demonstrated that the InterGard Silver graft is safe with no side effects. The primary patency rate was excellent, and the graft infection rate was low, despite a high incidence of nosocomial infections [100]. A comparison to show the efficacy of collagen silver-coated polyester and gelatin-sealed grafts with rifampin-soaked vascular grafts to resist infection from MRSA and *Escherichia coli* was carried out. The results indicate that collagen silver-coated grafts and gelatin-sealed grafts, both soaked in rifampin, provide resistance against MRSA and *E. coli*. There was a trend toward better resistance but without statistical significance against *E. coli* from the rifampin silver graft compared with the rifampin-soaked Gelsoft graft, without signs of inflammation from InterGard silver grafts [101].

Antibiotic retention on polytetrafluoroethylene (PTFE) grafts prepared using three antibiotic-bonding methods was compared following implantation into the arterial circulation. Ciprofloxacin or silver-ciprofloxacin was bonded to PTFE surfaces by surfactant-mediated or direct bonding methods. Bonding of silver-ciprofloxacin on PTFE grafts provided an effective source of local antibiotic release at levels which may be useful for bypass grafting in contaminated wounds or for in situ replacement of grafts infected by the central nervous system (CNS) [102].

Infection is a major complication in vascular stents. Stents impregnated with gelatin and dipped in Rifampicin have been shown to resist methicillin-resistant *Staphylococcus aureus* in both animal experiments and in man [103].

TYRX's AIGISRx, a commercially available antibacterial envelope for use with cardiac rhythm management devices (CRMD), and PIVITAB™, a new surgical hernia mesh licensed to C. R. Bard, both elute the powerful antibiotic combination of minocycline and rifampin [104].

5.4 Limitations of antibacterial materials

Antibacterial materials have been widely used clinically as medical devices, in which the active substances, such as antibacterial molecules, are present on or in the matrix of the surface of the devices, such as topical dressings for the management of wounds, including surgical, acute and chronic wounds, and burns, and implants, including long-term implants such as artificial joints, fixation devices, sutures, pins or screws, catheters, stents, and drains. Significant progress has been made in terms of the development of suitable biomaterials as carriers, the control of the release profile of the active substances, the antibacterial surface interaction with the system of the biological medium, the clinical efficacy, and, of course, the control of the manufacturing process of the final integrated device–medicine hybrids together with the regulatory issues for marketing biocides/devices, but there are still many limitations for development and application of antibacterial materials.

One limitation is the selection of the antibacterial substance, which can potentially lead to bacterial resistance. For example, the use of silver is increasing rapidly in the field of wound care, and a wide variety of silver-containing dressings are now commonplace, as reported in section 5.3.1 (wound care). However, concerns associated with the overuse of silver and the consequent emergence of bacterial resistances are being raised. In a review by Percival *et al.* [105], it is stated that although resistance to heavy metals, such as Ag^+, has been studied and reported, exact mechanisms are not known and there is little current evidence of emerging microbial resistance to silver. Unlike in the case of antibiotics, resistance to antiseptics, such as Ag^+, is rare and sporadic. Certainly, with widespread use of Ag^+ in wound care, more potential pathogens are going to be exposed to this agent. With the knowledge that silver-resistance genes exist sporadically in certain types of bacteria, it would be appropriate for future studies to determine the actual prevalence of these genes within clinical and environmental settings. Currently, knowledge is limited. Therefore, it is advised that the best approach is to keep hygiene emphasized in wound care and use wound

dressings with antibacterial materials targeted towards those applications which have demonstrable benefits [106].

Another limitation is the lack of an ideal controlled release system to minimize the cytotoxicity of antibacterial materials, which could potentially lead to the failure of the wound-healing process and tissue/implant integration, and to maximize the efficacy of the anti-infection property. For example, in a recent published paper reviewing the clinical evidence of use of Acticoat™ dressings in burns, there is evidence to suggest that Acticoat™ has improved bacterial clearance compared to other silver-containing dressings. It is easy to use, and has sustained release of silver, allowing less frequent dressing changes. This combined with its low toxicity levels make it a possible ideal dressing for burn wounds. However, despite the wide use of Acticoat™ in burns, the available evidence regarding its use in burns is weak, with only one study considered to be (level of evidence) LOE 1. More well-designed and properly reported, randomized, controlled trials are essential for informed clinical decision making [107].

According to Wittaya-areekul and Prahsarn [108], the ideal wound dressing should have the following properties: (i) provide a moisturized wound healing environment, (ii) provide thermal insulation, (iii) be removable without causing trauma to the wound, (iv) remove drainage and debris, (v) be free from particulate and toxic product, and (vi) promote tissue reconstruction processes. However, it is still difficult to get all these ideal elements in one single wound dressing, not mentioning the antibacterial function. Therefore, the factors in the material itself also limit the development of advanced antibacterial materials.

Another limitation is the difficulty in obtaining an ideal antibacterial substance, possessing all the following features:

- effectiveness against micro-organisms;
- cost-effectiveness in the end product;
- compatibility with ingredients of the final product;
- does not discolour the final product;
- can withstand high processing temperatures;
- effectiveness over a wide pH range;
- low toxicity to humans;
- extensive supporting documentation;
- high biodegradability

To bring a new antibacterial substance into the market with these features, the cost is very high. Manufacturers of active ingredients estimate that the cost for global registration is $5 million. It takes 2 years to conduct the toxicological testing and another 2–3 years for regional governments throughout the world to grant registration. End users will often want to evaluate the biocide over a 1–5 year test period. As a result of these

requirements and small potential market size, biocide manufacturers are extending product lines by turning to existing active ingredients for new applications instead of developing new molecules [55]. This would certainly limit the development of new antibacterial materials for clinical application.

Impending environmental regulations, both in Europe and elsewhere, present major challenges for suppliers of biocides. The European Union's (EU's) Biocidal Products Directive (BPD) and the flagship REACH chemicals policy will force the rationalization of many product lines, removing a large number of active ingredients from the market and requiring manufacturers to source replacement 'green' actives. In June 2007, the EU's Regulation (EC) No. 1907/2006 on the registration, evaluation, authorization and restriction of chemicals (the so-called 'REACH Regulation') entered into force. The REACH Regulation imposes sweeping requirements on both manufacturers and importers of chemicals and products containing them. In particular, REACH imposes new requirements on producers of medical devices, which are in addition to those of EU-specific medical device legislation. This will certainly add extra burden with respect to the development of antibacterial materials using antibacterial bioactive substance for medical device applications.

Another limitation is the consideration of the longevity of the effect of antibacterial properties. Using antibacterial materials does not mean it is not necessary to follow the general hygiene requirement for cleaning. For example, PVC flooring and wall coverings with an antibacterial additive have been promoted as 'hygienic surfaces' for hospital use. However, it should be stressed that it does not necessarily follow that as a result of antibacterial protection, these surfaces are no longer vulnerable to infection, and that conventional cleaning methods can be compromised, as the contamination is usually associated with the soiling of that surface with dirt, food, or bodily fluids. An 'ideal' in-dwelling medical device surface should have the same surface properties as that of a healthy living body, which would resist bacteria adherence, kill bacterial, and promote the growth of living tissues, but such in-dwelling medical devices are difficult to manufacture. Because the host-maintained immune defence system usually rejects a foreign body intrusion, and bacterial species are constantly changing, there are limitations in the device manufacturing process.

5.5 Future trends

It is expected that there will be a strong growth in the antimicrobial material industry, including plastics, implants, and other medical devices, for the following reasons [55].

- The market demands implants or other medical devices with anti-

infection effect, where the infection or other microbial contamination is a common factor, leading to the failure of implantation in clinics.
- The marketing advantages of value-added antibacterial products, which have generally met with consumer favour, and the need to ensure hygienic conditions in industrial, commercial, medical, and other institutional settings, will support further gains.
- Regulatory pressures on traditional antimicrobials, such as oxybisphenoxarsine (OBPA), 1-(1-phenylcyclohexyl) pipe (PCP), and tributyltinoxide (TBTO) promote the search for new, natural, green antibacterial substance.
- Increasing concerns related to disease transmission will drive demand for surfaces treated with antimicrobials.
- High-end industry growth in particular geographical regions, such as Asia.
- Growing use of antimicrobials as hygiene aids.
- Increasing use of plastics in new applications.

In the future, the development of antibacterial materials will focus on creating a surface that would not trigger the host defence system, possesses excellent biocompatibility, and can resist bacterial adherence or release antibacterial active substance in a controllable way. In addition, the antibacterial materials should be easy to make and possess high antibacterial activity together with a broad spectrum of antibacterial properties, fast recovery capability, and sustained delivery of antimicrobial agents [109].

The design of antibacterial materials will be mainly focused on surface treatments, as there are many advantages of surface treatment to incorporate anti-infective agents onto the surfaces of medical devices. These advantages include: a large variety of anti-infective agents on the surface can be selected; straightforward and inexpensive modification of existing devices is possible without changing the device bulk properties. For example, BIOSAFE® antimicrobial's active ingredient is a quaternary ammonium compound, made usable in plastics through organofunctional silane technology. BIOSAFE® is permanent, non-migrating, and non-toxic at a lower cost than silver-based additives. This could be an example of future antibacterial devices.

Continued efforts in the future will be required to advance the understanding of the pathophysiology of device-related infections and their effects on the functions of human homeostasis, such as the microstructure and chemical structure of the adherence mechanism, receptor sites in compromised tissue, and factors that might effectively block the initial bacterial adherence. The progress in these fundamental understandings will encourage the appearance of new technologies, which

will then provide superior anti-infective devices [110]. In addition, new technologies, including nanomedicine with antibacterial effects and tissue engineering for body repair, will generate great interest in clinical research.

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