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Antimicrobial surfaces and their potential in reducing the role of the inanimate environment in the incidence of hospital-acquired infections

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Environmental surfaces and their role in the epidemiology of hospital-acquired infections (HAIs) have become an area of great scientific interest, particularly in light of the much publicised cases of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* in UK hospitals. This feature article sets out to examine the role of surfaces and the inanimate environment in the spread of HAIs, and looks at various antimicrobial techniques being researched to reduce microbial contamination of surfaces. Preventative measures such as coatings which reduce initial microbial adhesion to surfaces will be considered alongside actively antimicrobial measures which inactivate microorganisms already adherent to a surface. The principal focus of this feature article will be given to light-activated antimicrobial surfaces such as the photocatalyst TiO_2 and surfaces with embedded photosensitisers. Surfaces which release antimicrobial compounds or metal ions such as silver and copper are also examined, alongside materials which kill microbes upon contact. The widespread research and development of these antimicrobial surfaces is of great importance in maintaining acceptable levels of hygiene in hospitals and will help to fight the spread of HAIs *via* the contamination of inanimate surfaces in the healthcare environment.

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Ivan P. Parkin

1. Introduction

This feature article focuses upon antimicrobial surfaces which might be deployed to reduce

microbial contamination of the inanimate environment, particularly in a healthcare setting, in order to help reduce hospital-acquired infections (HAIs). The primary focus is to cover antimicrobial coatings and surfaces for use outside of the human body, rather than those designed for use within the body. Antimicrobial surfaces for use in medical devices will only be briefly mentioned as this is a separate field in its own right, where the additional prerequisite of non-cytotoxicity to human cells is required. This review will firstly examine surfaces which resist microbial adhesion and which are antifouling. This will include established methodologies, such as poly(ethylene glycol) coatings, as well as some newly-developing techniques, such as thin films of diamond-like carbon and biomimetic surfaces. The second area of focus is that of actively antimicrobial surfaces—these are divided into categories of biocide-releasing surfaces (such as silver and copper ion release); surfaces which are microbicidal upon contact (for example polycationic coatings); and light activated antimicrobial surfaces (such as photosensitiser-containing polymers and TiO_2 photocatalyst thin films).

For some time scientists and healthcare professionals have believed in the importance of surfaces as reservoirs of microbes implicated in a wide variety of HAIs. Papers published as early as the 1960s[1] showed some initial evidence supporting the role of surfaces in the epidemiology of disease, but it was not until more recently that good quality evidence for this has become available.[2] It is perhaps the staphylococci, in particular methicillin-resistant *Staphylococcus aureus* (MRSA), that have received the greatest interest and indeed media attention. Various studies have examined microbial contamination and the survival of microbes in the hospital environment.

Bacterial infections such as those caused by MRSA are more common in hospital environments than elsewhere[3] and *S. aureus* is most commonly passed on by direct contact, usually by the hands of healthcare workers.[3–5] The spread of MRSA and other infectious agents can be controlled effectively through a rigorous hygiene regime. Simply washing ones hands is sufficient to help control the spread of MRSA,[3,6] but washing of the hands is of little use if the hospital environment is heavily contaminated.[4]

Surfaces may act as reservoirs of microbes which could in turn lead to the spread of infection upon being touched, by either healthcare workers or patients. Despite this however, there is currently little in the way of direct scientific evidence to link pathogens found on a particular surface with a specific manifestation of infection or disease.[4,5,7] The available evidence shows that i) common surfaces/articles within the hospital environment can become contaminated with pathogenic microbes and ii) hands (gloved or un-gloved) can become contaminated with these organisms after touching such a surface.

Studies have shown contamination of common hospital surfaces such as room door handles,[6] sterile packaging,[8] mops,[9] ward fabrics and plastics,[10] healthcare workers' pens,[11] keyboards and taps,[12] stethoscopes[13] and telephones[14] by potentially harmful microbes. In addition to this, there is mounting indirect evidence of a link between contaminated surfaces and nosocomial infection.[7,15,16] Boyce *et al.*[15] found that contamination of the inanimate environment with MRSA occurred when either infected or colonised individuals were present in hospital rooms. More significantly, it was found that 65% of nursing staff that had directly treated an infected individual contaminated their gowns/uniforms with the organism. MRSA contamination of gloves was also observed in 42% of personnel who had no direct contact with the patient, but had touched surfaces in infected patient's rooms. The studies of Boyce *et al.*[15] and Bhalla *et al.*[16] both clearly demonstrate how the hands (gloved or otherwise) of healthcare workers can become contaminated, presumably by touching surfaces in the immediate vicinity of an infected patient.

Combining knowledge of pathogen survival on surfaces, and the evidence for transmission of pathogens from surfaces to hands, the importance of the inanimate hospital environment as a reservoir for nosocomial pathogens such as MRSA can be seen. It is not surprising for the link between surface contamination and nosocomial infections to have been demonstrated, particularly when MRSA, for example, can survive for up to 9 weeks if it dries on a surface, or 2 days when on a plastic laminate surface[5] and is stable in varying conditions of temperature, humidity, exposure to sunlight and desiccation.[17]

One area that is still under investigation is the determination of typical surface contamination levels, and quantification of a minimum infective dose at which a contaminated surface becomes a problem to health. There have been numerous studies of microbial contamination of surfaces in the hospital environment (Table 1)—what can be said about this is that there is great variation in colony forming units (cfu) recovered per unit area.

Table 1 Some typical bacterial loads for healthcare and food industry related surfaces. Note: many of the values have been derived from other measures, including $\log_{10}$ cfu/cm^2 and total aerobic colony count on RODAC/contact plates. Where conversions and derivations have been performed the cfu/cm^2 value is to the nearest whole cfu

Field of Study	Site	Bacterial Load	Reference and Year
Healthcare	Hospital ward surface	<3 cfu/cm^2	Rutala *et al.* 1983[18]
	Ward floor	<5 cfu/cm^2	
Healthcare	Stethoscope membrane	In >54% of cases >5 cfu/cm^2; in 18% of cases >29 cfu/cm^2	Bernard *et al.* 1999[19]
Healthcare	Hospital ward surfaces	2.5 to 40 cfu/cm^2; ward cleaning reduced this to <2.5 cfu/cm^2	Griffith *et al.* 2000[20]
Healthcare	Hospital kitchen surfaces	2 to 294 cfu/cm^2	Aycicek *et al.* 2006[21]
Healthcare	Nurse workstation	<9 cfu/cm^2	Hardy *et al.* 2007[22]
	Under ward bed	<25 cfu/cm^2	
Healthcare	Hospital ward surfaces	55 to 80% of sampled sites had >5 cfu/cm^2	White *et al.* 2007[23]
Food	Meat preparation surfaces	10^5 cfu/cm^2	Upmann *et al.* 1998[24]
Food	Vegetable preparation surfaces	>10^5 cfu/cm^2	Kaneko *et al.* 1999[25]
Food	Abattoir surfaces	8 to 1.3 × 10^4 cfu/cm^2	Grosspietsch *et al.* 2006[26]
Food	Refrigerator surfaces	813 to 6 × 10^8 cfu/cm^2	Jackson *et al.* 2007[27]
Food	Food contact surfaces	630 to 1.8 × 10^9 cfu/cm^2	Gounadaki *et al.* 2008[28]

Currently there is no microbiological quality control standard for surface hygiene in general hospital ward areas—this is quite surprising and there is an obvious need for this to be developed. Surface hygiene standards have been proposed,[4] and these are based on two standards: 1) the monitoring of so-called "indicator organisms" and 2) the total aerobic colony count in a sampled area. The first standard concerns monitoring the clinical area for microbes of clinical importance, for example *S. aureus*, *Clostridium difficile*, and vancomycin-resistant enterococci (the "indicator organisms")—a surface contamination standard for these organisms is proposed at <1 cfu/cm^2.[4] The second standard concerns the total aerobic colony count (ACC)—this is a non-selective assay of the aerobic organisms sampled from a test area. Standards for the total ACC already exist for food processing plants in the US and Sweden, the threshold being <5 cfu/cm^2 and this threshold is suggested for hand contact surfaces in hospitals.[4] There is, however, no evidence regarding what level of surface contamination is hazardous, and the infective dose for MRSA varies from study to study and on a patient-to-patient basis.[2] In general, the number of cfu required to initiate an infection by MRSA lies in the

very broad range of between 10 and several million.[2] It would be exceptionally challenging to design an experiment to assess the minimum infective dose from a known surface contamination and to date this has not been reported. What is clear is that when it comes to the level of surface contamination, particularly in a healthcare environment, the lower the microbial load the better.

By considering the evidence regarding surfaces and the epidemiology of disease in the hospital environment, a scheme can be proposed to represent the situation in a typical hospital environment (Fig. 1). Surface contamination may arise in a number of ways, but in particular we can see how it may be due to direct transfer (by touching) from an infected or colonised patient, or from a healthcare worker who is carrying the pathogen on their hands. Once a surface has become contaminated, a cyclical problem exists since this contamination can now be propagated to other surfaces and patients in the vicinity. Whilst appropriate hand washing by healthcare workers can control the further spread of the microorganism *via* hand–surface transmission,[6] it cannot eradicate the surface contamination itself, nor the potential direct transfer by the patient, and the cycle will always remain. The efficacy of traditional cleaning methods to remove surface contamination is under debate. A recent study of MRSA contamination in the hospital environment detected MRSA on 74% of swab samples prior to cleaning, and on 66% of swab samples after cleaning.[29] In order to fully tackle the situation, it is clear that a bioactive surface—which can either prevent bacterial contamination altogether, or destroy adherent organisms—is required.

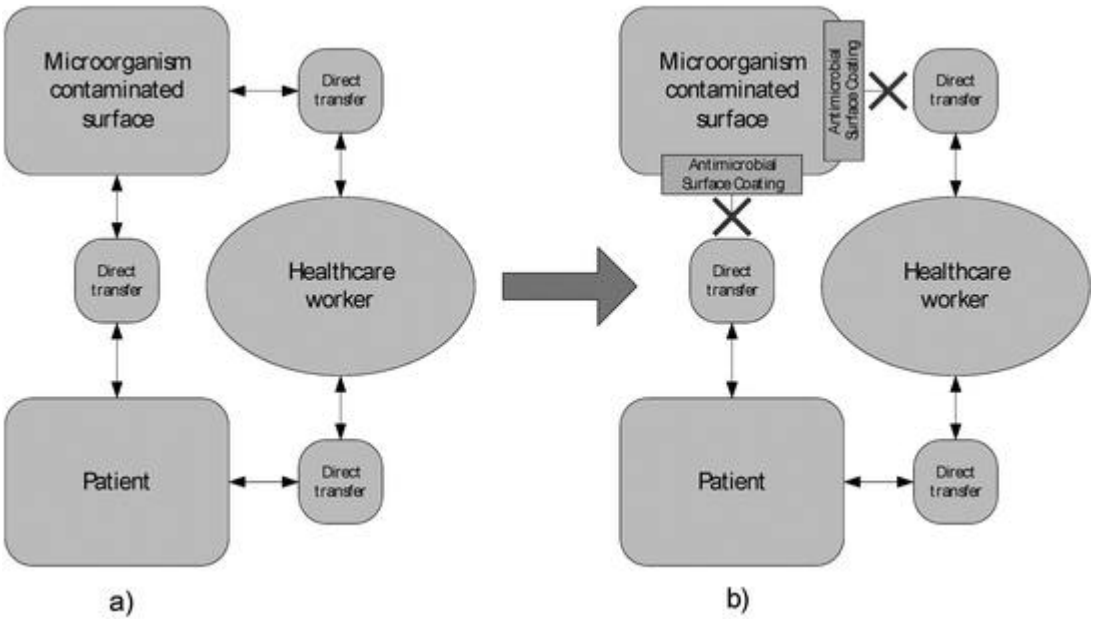


Fig. 1 The role of surfaces and antimicrobial surface coatings in the epidemiology of HAIs—beating the "nosocomial infection loop".

The development of actively antimicrobial surface coatings can play an important role in tackling the problems highlighted by the cyclical nature of Fig. 1a. Such a coating would be able to reduce microbial loads on a surface without outside intervention and hence would play a part in reinforcing the hygiene regime of a clinical environment. By removing the ability of a surface to act as a microbial reservoir it may be possible to break this "nosocomial infection loop"; this leaves the problem of person–person transmission—which can be addressed by appropriate hand washing and the use of alcohol hand rubs by healthcare workers. Hospital acquired infections are estimated to cost the NHS up to £1000 million per annum,[30] but the proportion of this cost resulting from surface contamination, such as on a catheter, is undetermined.[31] It is known however that catheter related infections are found in around 10 to 50% of catheterised patients and that for each day of catheterisation, the risk of developing a

urinary tract infection (UTI) increases by 10%.[32] This essentially means that all patients with long term indwelling catheters will develop a UTI as a result of catheterisation. In the USA each catheter related infection, on healthcare costs alone, averages $20000 per episode.

2. Antifouling and anti-adhesive coatings

One approach to microbial contamination of surfaces is to prepare a surface to which microbes find it hard to become attached. The strategy of this technique is to prevent microbial adhesion to the device or surface in the first place. As such this is a preventative strategy.

2.1 Poly(ethylene glycol) coatings

One well established method for preventing the adhesion of microbes, proteins and mammalian cells to surfaces is to coat them with a layer of poly(ethylene glycol), or PEG. PEG modification of polyurethane surfaces was first shown to inhibit microbial adhesion in the late 1990s, with much research being carried out in this area subsequently.[33–36] The current methodology involves the deposition of a self-assembled monolayer (SAM) on a substratum (usually a gold surface), followed by functionalisation of the SAM to contain the required PEG functionality. PEG polymeric surfaces are antifouling because of firstly the hydrophilic interaction with the otherwise hydrophobic microbial cell envelope, which does not favour microbial attachment to the surface. The second reason for the antifouling properties lies in the dynamic movement of the PEG chains tethered to the surface, coupled with their lack of binding sites—these factors making it more difficult for a microbe to become attached to the surface. PEG, and modified PEG surfaces, have been shown to effectively inhibit the adhesion of microbes by up to a 3 log unit reduction in attached microbes (as well as a reduction in adherent proteins and mammalian cells). The principal drawback of this technology is that currently the deposition of a PEG surface requires 3 synthetic steps and can only be done to a surface during manufacture.[35]

2.2 Diamond-like carbon films

Diamond-like carbon (DLC) films are comprised of metastable, amorphous carbon with significant sp^3 character (a-C) comprising small quantities of hydrogen—hence the films are sometimes known as amorphous hydrogenated carbon (a-C:H).[37–39] First prepared by an ion-beam technique in the 1970s,[40] these materials are now more commonly produced in the laboratory by plasma assisted/plasma enhanced chemical vapour deposition (PA/PECVD).[38,41] A plasma of atomic hydrogen is used, which prevents the deposition of sp^2 carbon in the form of graphite and allows deposition of sp^3 carbon in a diamond-like thin film.[38,41] The hydrogen plasma is therefore the source of the hydrogen which becomes deposited, up to *ca.* 60%, within the a-C:H film.[37] Other deposition methods include sputtering, cathodic vacuum arc and pulsed laser.[37,38]

DLC films exhibit many of the useful characteristics of bulk diamond, such as very low friction coefficients, high wear resistance, chemical inertness and optical transparency, but are significantly cheaper and more facile to manufacture than the bulk material.[37,38,42] The physical and mechanical properties of these films, especially in the study of their tribology, meant that initial uses were as protective coatings at the interfaces between the magnetic storage platters and the read/write heads of hard disk drives.[37] However, researchers have subsequently realised many other uses, in particular that of DLC as a biocompatible surface coating for biomedical devices such as stents or replacement joints.[39,42,43] Liu *et al.* reported that a DLC film can reduce the adhesion of various microbes to a stainless steel substrate, and by doping the DLC with Si or N, this can be reduced even further.[42,44,45] Reduction in microbial adhesion of up to approximately 6×10^6 cfu/cm^2 has been reported for *Pseudomonas aeruginosa* under static conditions on an Si-doped DLC surface against a stainless steel control.[44] It is interesting to note that these surfaces contain no active antimicrobials, but DLC films may be doped with microbicidal species such as Ag or Cu, yielding antimicrobial properties in addition to the anti-adhesive properties.[43] This represents a very interesting and new area of research, and doped

DLC coatings may be very useful to prevent infections due to invasive biomedical devices such as venous and renal catheters, which are a major source of HAIs in the UK.

2.3 Easy clean surfaces—prevention of microbial adhesion

Water droplet contact angle is a measure of surface energy (*i.e.* hydrophilicity or hydrophobicity) that can be used as an indicator of how easy it is for a microbe to colonise a surface.[46] The contact angle is the angle subtended by the water droplet on the surface. For self-cleaning surfaces, either an exceptionally hydrophilic (less than 10° as observed in the photocatalytically self-cleaning glasses such as Pilkington Activ™[47,48]) or a hydrophobic (>140°) surface is required. Intermediate contact angles of 30–100° do not have easy clean features and are significantly easier for microbes to stick to, and possibly form a biofilm.[49] Very smooth surfaces are, in general, harder to colonise than rough surfaces—though surface roughness is often required to obtain very high contact angles. Nature uses rough surfaces on some plant leaves to produce a self-cleaning surface known as the lotus effect.[48] The lotus effect is where water droplets on the surface of the plant leaves have exceptionally high contact angles, typically greater than 140°, and these droplets roll and spin across the surface at very low tip angles (5° or less). The spinning action picks up dirt, dust, bacteria and viruses from the leaf surface with remarkable effect. Lower contact angles encourage water droplets to slide across the surface, the sliding action is inefficient at removing the microbes. Man-made replicates of the lotus effect are widespread, however these have yet to be adopted in the hospital environment.[50,51] Page has shown the effect hydrophobicity can have on bacterial adhesion, with strongly hydrophobic commercial coatings such as Pilkington Hydrotech (130° contact angle) showing marked bacterial shedding properties compared to glass controls and other commercial coated glass products.[52] In this work, the hydrophobic materials were shown to significantly reduce microbial adhesion to a sample submerged in a microbial suspension and subsequently removed for analysis. The principle drawback of the hydrophobic easy clean materials is that whilst preventing microbial contamination in the area treated, it does not address the problem of pathogenic microbes which are incident upon the surface—it merely moves them elsewhere, where they will have to be dealt with by other microbicidal techniques. The photocatalyst based easy clean coatings however, have a dual functionality—hydrophilicity leads to water sheeting and ease of cleaning, and the photocatalysis can also destroy any adherent microbes. The photocatalyst type materials will be considered further in section 3.3.2.

2.4 Zwitterionic polymer biomimetic surfaces

Recently it has been shown that polymers with zwitterionic head groups can be applied as surface coatings which inhibit biofouling of the surface. Polymers which have received research interest are poly(phosphorylcholine) polymers,[53–55] poly(sulfobetaine) polymers[56] and poly (carboxybetaine) polymers.[56] The initial discovery was that these zwitterionic surfaces are biocompatible and non-thrombogenic. The biocompatibility results from the zwitterionic nature of the polymer headgroup (see Fig. 2 for a typical example) that mimics that found in the lipid bilayers of biological membranes.

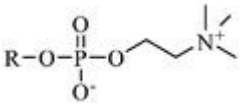


Fig. 2 The phosphorylcholine polymer headgroup—a typical example of a zwitterionic polymer used in biomimetic surface coatings, which exhibit reduced microbial adhesion.

The latest studies[54,56] have shown that these zwitterionic surfaces prevent initial bacterial adhesion, and that biofilm formation is significantly arrested. It is postulated in the studies that

the principal reason for this is that the zwitterionic head can associate a large amount of water—making the material essentially hydrophilic. This leads to reversible interactions between incident microbes and the surface—discouraging adhesion of cells, both mammalian and microbial. These zwitterionic surfaces demonstrate promise for coating medical devices such as catheters, because their biomimetic nature firstly affords biocompatibility by reducing attachment of human cells to the device (which can cause encrustation) and secondly afford protection against bacterial biofilm formation which can lead to device-related infections. This technology is relatively new but will no doubt receive further research interest in an attempt to reduce infections caused by indwelling biomedical devices. However, these types of surfaces, like the easy clean technologies discussed in section 2.3, still do not fully address the problem of microbial contamination as they have no antimicrobial functionality.

3. Antimicrobial coatings and surface technologies

There are a wide variety of antimicrobial coating technologies which are either currently available as marketed products, or in research stages. Some of these technologies are organic antimicrobials, released from the product (for example Microban® which contains Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol) as the antimicrobial agent), whereas others rely on inorganic antimicrobials—most commonly the silver ion, Ag^+. These techniques which utilise diffusible antimicrobials have the potential problem of inducing microbial resistance, because the products continually deliver active compounds to the environment. Increased exposure of microbes to these compounds will inevitably lead to increased occurrences of resistance to the treatments, though at present there are few organisms which display resistance to Ag or Cu.

3.1 Microbicide-releasing surfaces

One of the most heavily marketed and most widespread products for suppressing microbial growth is Microban®.[57] Microban® incorporates Triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol)—a broad spectrum phenolic antimicrobial—into a surface, normally a polymer. It works more like a disinfectant, *i.e.* killing outside in, rather than an antibiotic, *i.e.* inside out. With a Microban® product, the antimicrobial leaches from the surface of the product to perform the antimicrobial function. This means that effectively they are non-permanent. Triclosan is found in many products such as hand wash soaps, toothpastes as well as on touch surfaces and items like chopping boards and cling film. Microban® has been shown to suppress bacterial growth within the domestic, especially kitchen, environments; however it is not widely used within hospitals. One of the first uses of Microban® as an antimicrobial in a UK hospital was at the John Radcliffe in Oxford at the end of 2006, where it was used as a coating on door handles.[58] There has also been significant concern about possible development of Triclosan resistance; furthermore some studies suggest that Triclosan can, under the action of UV light, produce dioxins, which are extremely hazardous to man.

3.1.1 Silver and silver-containing surfaces. Silver has long been known to be an antimicrobial, the Greeks and Romans used silver coins and vessels to make drinking water potable.[59] More recently in the 1900s 1% silver nitrate solution was commonly applied to the eyes of newborns to prevent infections that lead to blindness.[59,60] Ag^+ ions have a significant antimicrobial effect and have found uses in a number of commercial applications, documented in a recent review.[61] These include the silver sulfadiazine creams, successfully applied topically to burns patients. This cream consists of 1% silver sulfadiazine and 0.2% chlorhexidine digluconate[61] and is effective as a result of the synergistic action of these antimicrobials. Silver has also been successfully used in wound dressings and as an additive in catheters and other medical devices.[61] When it comes to available commercial coating products; AgION Technology's AgION™[62] and AcryMed's SilvaGard™[59] are two of the more well known. Both of these silver-containing products rely on the diffusion of Ag^+ ions from the substrate material and their subsequent action on adherent microbes as broad spectrum antimicrobials. To date, few organisms have developed resistance towards the silver ion as an antimicrobial. It is widely

believed that the effectiveness of Ag^+ as an antimicrobial is due to its ability to bind with thiol (–SH) groups on proteins and enzymes—thereby inactivating them.[60] Despite the initial effectiveness of these existing antimicrobial coatings, they have one major drawback—they are non-permanent, relying on diffusible antimicrobials to which microbes can develop resistance, however the concentration of Ag^+ required for action is actually very low and varies between reports. One possible drawback of silver based antimicrobials is the possibility of Ag ion cytotoxicity towards mammalian cells, as recently reported.[63] This could be an area of concern for antimicrobial devices or treatments coming into contact with human cells and tissues perhaps in a biomedical device.

3.1.2 Copper and copper alloy surfaces. Like silver, copper has long been considered to be a hygienic material. It has been known since the 1980s that copper, along with other heavy metals such as cadmium and lead, is toxic to microbes,[64] and it was suggested by at least one researcher that brass touch surfaces, such as doorknobs, be maintained in hospitals instead of the stainless steel replacements.[65] It was only more recently that copper and its alloys have been thoroughly investigated as antimicrobial surfaces. Keevil[66–70] has assessed the antimicrobial activities of copper and some of its alloys in comparison with stainless steel. Keevil's group has assessed a number of microbes of clinical importance, including MRSA,[67] *E. coli* O157,[66] *Listeria monocytogenes*,[68] *C. difficile*,[70] and Influenza A virus.[69] In all experiments, the copper surfaces clearly exerted an antimicrobial effect, as did the majority of the copper alloys. Stainless steel was shown to be inert compared to the coppers. The studies with MRSA, *E. coli* O157 and *L. monocytogenes* were carried out on 1 cm^2 coupons of material, inoculated with 10^7 cfu of the test organism. On pure copper substrates the inocula were reduced to a level at or below the experimental detection limit (100 cfu) within 90 minutes or less at 20–22 °C.[66–68] Vegetative cells and spores of *C. difficile* were also effectively killed by the copper coupons, with complete kill in 24 to 48 hours. Stainless steel coupons showed no change in bacterial load, even after 1 week of exposure.[70]

The work of Keevil's group shows that, despite its association with hygiene, stainless steel surfaces may not be the best choice for areas where microbial surface contamination is an issue. Whilst it is an easy material to clean, stainless steel has no ability to reduce the microbial load on its surface. Despite its excellent antimicrobial response however, copper may not be a suitable replacement for stainless steel in a hospital environment. This is because of its mechanical properties in comparison with stainless steel and the fact that it oxidises when exposed to the air. However, as Keevil has shown, copper alloys, such as brass, also exhibit antimicrobial activity, albeit of smaller magnitude. These alloys have improved aesthetic and mechanical properties and may be more suited to real world applications. A clinical trial of copper and copper alloy fixtures and fittings is currently under way in Selly Oak Hospital, Birmingham, UK.[71,72]

3.1.3 Bacteriophage-modified surfaces. Bacteriophages are viruses that infect prokaryotic cells. Phages usually target individual species of bacteria, bind to their surface, inject their genetic material and replicate within the bacterial host. If the replication of the phage is by what is known as a "lytic" process the eventual result is the lysis of the host cell, and the release of more phages.[73,74] The replication process is self propagating until there is no more host organism available. As a result of this, lytic bacteriophages make interesting candidates for antimicrobial use. Stone[75] details the recent development and use of a phage-containing wound dressing containing lytic bacteriophages. The dressing was used successfully in the treatment of some skin infections that were not responding to conventional antimicrobial therapy. The papers which document these results fully[76,77] acknowledge that the trials were not rigorously controlled and double blind, but it is clear from the results that the treatment does appear to work well, although adequate clinical trials are needed.

The concept of modifying a surface with bacteriophages in order to produce an antimicrobial surface is a very recent development. Curtin *et al*. demonstrated how this could be done successfully on a hydrogel-coated silicone catheter model in 2006.[78] Indwelling catheters are a major route by which bloodstream HAI can occur, and numerous methods are being developed

to combat the formation of microbial biofilms on these devices, including some which have already been discussed, such as silver loading. In the work of Curtin *et al.*[78] the formation of a *Staphylococcus epidermidis* biofilm on catheters pre-treated with coagulase-negative staphylococcus phage 456 was monitored. It was shown that this modified surface, containing phage units, reduced biofilm formation significantly. With phage 456 and $MgCl_2$ or $CaCl_2$ supplements, a 4.47 log reduction in the mean viable count per cm^2 of substrate was recorded over 24 hours relative to a control having 7.01 log cfu/cm^2. A 2.34 log reduction was recorded when the supplements were not used.

A phage-modified surface is certainly an interesting antimicrobial approach, in particular because organisms currently resistant to antibiotics do not show resistance towards phages. Equally, because it theoretically only needs one phage to infect a host cell for a cascade in phage production, it could be a very efficient way of disinfecting a surface without significantly deactivating the surface in the process. There are, however, a number of potential problems. The first is the inherent specificity of the phage for individual bacterial species. Whilst this is excellent for a targeted *in vivo* therapy, it is less useful for a surface, where a number of different organisms, not necessarily just bacteria, may be present. A combination of phages would have to be used to increase the spectrum of activity, but this may leave out potentially harmful organisms. One other area of concern is that of phage resistance—bacteria can become resistant to a phage through mutations which change the susceptibility of the cell wall to the phage enzymes used to enable injection of genetic material.[74,75] Whilst it is believed to be easier to deal with resistance to phages by selecting new phages from cultures that maintain virulence[75] it is still a concern. Phage-treated surfaces or products would have to be constantly monitored and their formulation modified to remain efficacious—which will no doubt cause problems for regulatory approval.

3.2 Polycationic antimicrobial surfaces

Surfaces with cations deposited upon them were shown to kill microbes upon contact in the 1980s.[79] More recently surfaces treated with hydrophobic polycations were demonstrated to kill microbes in a similar manner upon contact with the treated surface by causing physical damage to the microbe's cell envelope.[80] The basic premise of these materials is to target microbes by taking into account two features of the microbial cell envelope—namely that they are hydrophobic and negatively charged. By depositing a coating consisting of hydrophobic polymer chains, interaction with the microbe cell envelope is favoured, however, the polymer chains will not tend to stand erect from the surface to interact with an incident microbe without some form of repulsive interaction between chains. To this end, a positively charged moiety is required—this keeps the hydrophobic chains separated and erect from the surface, and also electrostatically attracts microbes, due to the net negative charge on their surface. In effect, these materials attract a microbe towards the treated surface, resulting in the puncturing of the microbial cell envelope, and subsequent death of the cell. The most recent surface coatings of this type are polyethyleneimines (PEIs) and two examples are given in Fig. 3. These types of surface have been shown to be effective against a variety of microbes, including *S. aureus* and some viruses.[80–83] Whilst these PEI coatings are described as being permanently microbicidal, their mechanical stability and longevity have not been described and it is still yet to be seen how well they might respond to the rigours of use and indeed cleaning in a clinical setting.

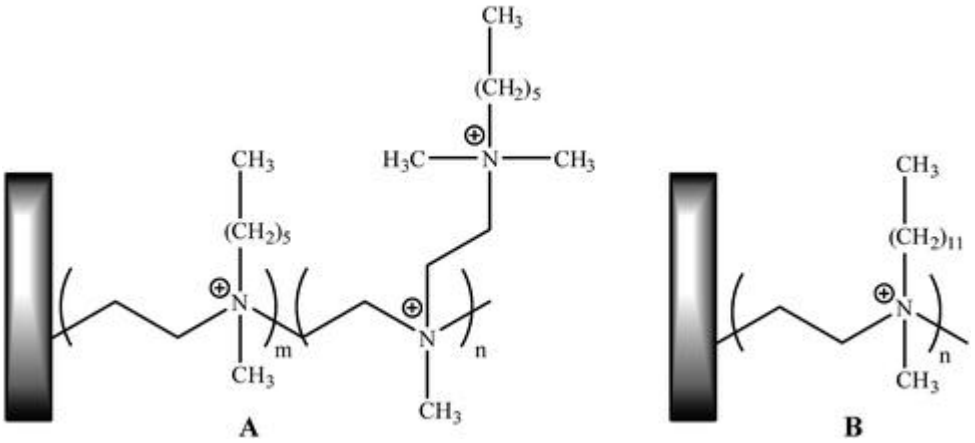


Fig. 3 Polycationic PEI antimicrobials. Branched *N*-hexyl,*N*-methyl-polyethyleneimine (A) and *N*-dodecyl,*N*-methyl-polyethyleneimine (B).

3.3 Light-activated antimicrobial agents (LAAAs)

An alternative method of disinfecting a surface is by the use of a coating that produces reactive radical species. Radical species, unlike the antimicrobials previously discussed, have no specific target within a microbe, that is to say they are completely non-selective microbicides.[84,85] This has one very important implication—it avoids the potential problems of microbes developing resistance to a microbicidal treatment, since there is no one site within a microbe upon which they act.[84] Resistance only develops when a specific site is targeted by a microbicide.

There are two principal coating types that produce these reactive species and act as antimicrobial surfaces: 1) a coating comprised of a photosensitiser immobilised in a coating and 2) a titanium dioxide based photocatalyst coating. These materials fall under the broad classification of light-activated antimicrobial agents (LAAAs).

3.3.1 Photosensitiser antimicrobials. The use of a photosensitiser as an antimicrobial agent is a direct refinement of the technique of photodynamic therapy (PDT). PDT is a commonly used therapy to target and destroy cancerous tissues. PDT is a form of indirect phototherapy,[86] in which light is used as a means of activating the curative agent—the photosensitiser. The photosensitiser is most usually administered systemically, but is so designed as to accumulate preferentially in the region of cancerous growth. The tumour area, complete with accumulated photosensitiser, is then illuminated with visible light, and the therapeutic process begins.

The mechanism of photoexcitation of the photosensitiser in PDT is shown in Fig. 4. The photosensitiser, in a singlet ground state (S_0), is photoexcited to the first excited singlet state, electron spins paired ($^*S_1$) by visible light incident on the photosensitiser. This excited state can either relax to the ground state *via* fluorescence (F), or it may undergo an intersystem crossing (ISC) to a triplet excited state with the electron spins unpaired ($^*T_1$). It is this triplet state which leads to the therapeutic effects of PDT, as there are two available pathways of reactions. The Type I reactions involve electron transfer and result in the production of radicals such as superoxide and the hydroxyl radical. The Type II reactions involve energy transfer from the triplet excited state, as it relaxes back to the ground state. Energy is typically transferred to ground state triplet oxygen, which is excited to a singlet state.[86] Principally, it is the production of singlet oxygen by the Type II process which is thought to act upon the cancerous cells, but the reactive oxygen species (ROS) produced by the Type I process are similarly destructive to cells.[86]

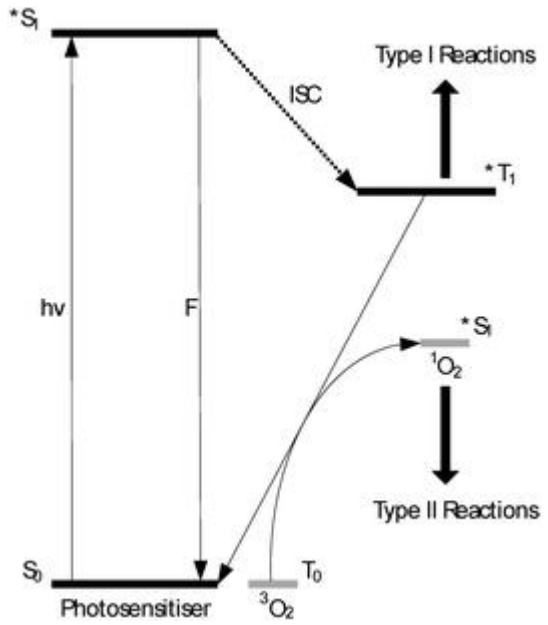
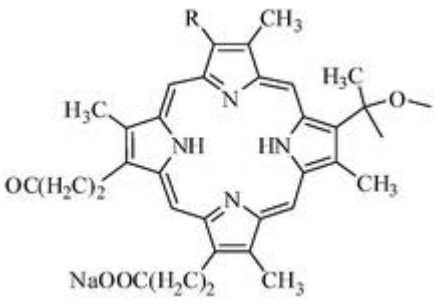
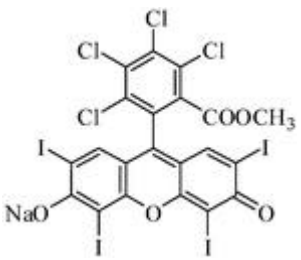
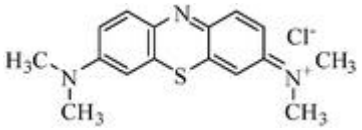
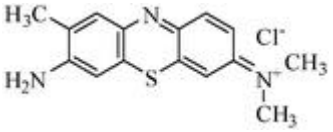


Fig. 4 Jablonski diagram showing energetic transitions from a photoexcited photosensitiser molecule to molecular oxygen ($h\nu$ = incident visible light energy, F = fluorescence, ISC = intersystem crossing).

In PDT the photosensitiser is chosen such that it preferentially accumulates in the cancerous tissue, and such that its absorption is at a convenient wavelength for the surgical equipment. The first PDT agents were porphyrins and phthalocyanines but other chromophores, such as the phenothiazines (*e.g.* methylene blue and toluidine blue (TBO)), have been studied. A selection of photosensitisers studied for both cancer and antimicrobial PDT are shown in Table 2.

Table 2 Some common photosensitisers employed in anticancer and antimicrobial PDT

 Photofrin®	 Rose bengal
 Methylene blue	 Toluidine blue O (TBO)

The destructive power of the radicals produced by photosensitisers can be put to use in a microbicidal surface coating when the photosensitiser is immobilised within a polymer matrix and applied to a surface.[84,87] In the recent work of Wilson[84] and Decraene *et al.*[87] photosensitisers such as toluidine blue and rose bengal were immobilised in a cellulose acetate coating. It was shown that the photosensitisers did not leach from the cellulose acetate matrix and produced a microbicidal surface active under visible (white) light conditions. The coating

materials were shown to be highly effective against a wide variety of microbes of clinical importance, such as *S. aureus*, *E. coli*, *C. difficile*, *Candida albicans* and *Pseudomonas aeruginosa.* The key benefits of this antimicrobial surface are that it can reduce microbial loads on a surface using visible light and avoids the problems of microbial resistance. There is, however, a potential disadvantage, in that the ROS produced by the photosensitiser could, in the long term, degrade the matrix containing the photosensitiser.

Parkin *et al*.[88] have shown that methylene blue (MB) and toluidine blue together with nanoparticulate gold can be incorporated into common catheter polymers such as polysiloxanes and polyurethanes. They have shown that these polymers have equivalent mechanical properties to polymers without the LAAA and that under hospital lighting or room lighting conditions these polymers show minimal degradation (10% photobleaching) over six months. The antimicrobial properties of the polymers were determined using a low power 632 nm laser radiation (He–Ne) against MRSA and *E. coli.* Samples tested for their antimicrobial properties were: the polymer without methylene blue or gold (MB- Au-); polymer with methylene blue only (MB+ Au-); polymer with gold only (MB- Au+); and polymer with methylene blue and gold (MB+ Au+). The results were dramatic. On very short exposure times of 2–10 minutes there was significant kill of both *E. coli* and MRSA for the polymers that contained some embedded MB and no detectable kill for the bare polymer or the polymer that contained only gold nanoparticles. The most pronounced bacterial kill was from the MB+ Au+ polymer. Against *E. coli.* a 1.5 log reduction in bacterial count was observed after 10 minutes of irradiation of the MB + Au- sample, no kill was seen in the dark, or for the irradiated bare polymer. The kill of *E. coli* was greater for the MB+ Au+ sample with a 2.0 log reduction after ten minutes irradiation, with again no detectable kill from the control. The nanoparticulate gold was found to synergistically enhance the observed kill from MB-incorporated polymers whilst having no direct antimicrobial property. The effect of the MB and MB+ Au+ polymer on MRSA was even more pronounced. For the MB+ Au+ sample, a greater than 3.5 log reduction in MRSA concentration was seen after 5 minutes of irradiation. In fact, after that time, the bacterial count was below the detection limit, whereas the dark control and blank polymer under irradiation showed no measurable kill.

3.3.2 Titanium dioxide antimicrobials. The efficacy of titanium dioxide (TiO_2) semiconductor particles as a means of disinfection was first realised in 1985 by Matsunaga and co-workers.[89] In this first study it was found that platinised TiO_2, when irradiated with ultra band gap UV radiation (wavelength less than approximately 387 nm), acted as an antimicrobial agent being 100% effective against 10^3 cfu/ml *Saccharomyces cerevisiae* and 10^3 cfu/ml *E. coli* after 2 hours UV illumination. No inactivation of the microbes was observed when the UV light was used in the absence of the TiO_2 photocatalyst. Photodisinfection was rationalised as a result of photocatalytic processes taking place on the TiO_2 surface. Ever since this discovery, research into the efficacy of TiO_2 antimicrobials has centred on three areas of interest: how TiO_2 acts as a photocatalyst; how microbes are killed by the TiO_2 surface; and how the surface can be made more efficient at killing microbes.

The first two areas of interest have been extensively studied and the modes of action are very well understood, in terms of both how photocatalysis occurs and how this leads to the killing of microbes.

The titanium dioxide formed after purification is one of two crystalline forms, anatase or rutile. Rutile is the most common of these forms as it can be produced from anatase at high temperatures. When employed as a photocatalyst in antimicrobial research, TiO_2 has often been used in the “as manufactured” form. The so-called gold standard of preformed TiO_2 used in a considerable amount of antimicrobials research is Evonik Industries (formerly Degussa) P25.[90–97] Indeed, the very first demonstration of antimicrobial activity of TiO_2 by Matsunaga *et al.* was performed using P25 suspensions.[89,98] P25 is a highly dispersed preparation consisting of both anatase and rutile titania in an 80:20 ratio, with a very high specific surface area of 50 ± 15 m^2/g.[99,100] Many researchers opt to make the TiO_2 materials themselves, often as thin films. The

two most common deposition methods for this are chemical vapour deposition (CVD) and sol-gel.[100]

3.3.2.1 Titanium dioxide photocatalysis. Titanium dioxide is well known to be a semiconductor. In the anatase form, it has a band gap energy (E_g) of 3.2 eV.[101] Irradiation of anatase TiO_2 with UV radiation greater than E_g causes promotion of an electron from the valence band to the conduction band. This results in the formation of an electron-hole pair. This is a free electron (e^-) in the conduction band, and a hole (h^+) in the valence band.[85,90,98,101] These reactive species then participate in oxidation and reduction processes either within the TiO_2 itself (electron and hole recombination), or with adsorbates at the surface. This is shown in Fig. 5. This is the key mechanism of titanium dioxide photocatalysis, since it produces reactive species at the catalyst surface. The principle reactive species is the hydroxyl radical, which is produced by redox reactions between photoexcited TiO_2 and adsorbed H_2O, molecular oxygen and from hydroxide groups on the catalyst surface.[85] Scheme 1 details the production of reactive species at the catalyst surface. The hydroxyl radicals produced by the redox processes at the TiO_2 surface are highly reactive and completely non-selective. These attributes make the radical species extremely potent biocides,[85] with the ability to oxidise most organic compounds at the catalyst surface.[90] Scheme 1 highlights a common misconception about photocatalysis, in that light energy is actually a reactant and is not strictly a catalyst. It is more correct to say that TiO_2 acts as the catalyst in a photosensitised heterogeneous catalysis.

$$TiO_2 + h\nu \rightarrow e^- + h^+$$

$$h^+ + H_2O_{(ads)} \rightarrow HO^\bullet + H^+$$

$$h^+ + OH^-_{(surface)} \rightarrow HO^\bullet$$

$$e^- + O_2 \rightarrow O_2^{\bullet -}$$

$$2O_2^{\bullet -} + 2H_2O \rightarrow 2HO^\bullet + 2OH^- + O_2$$

Scheme 1 Reactive radical species generated by TiO_2 photocatalysis.[85]

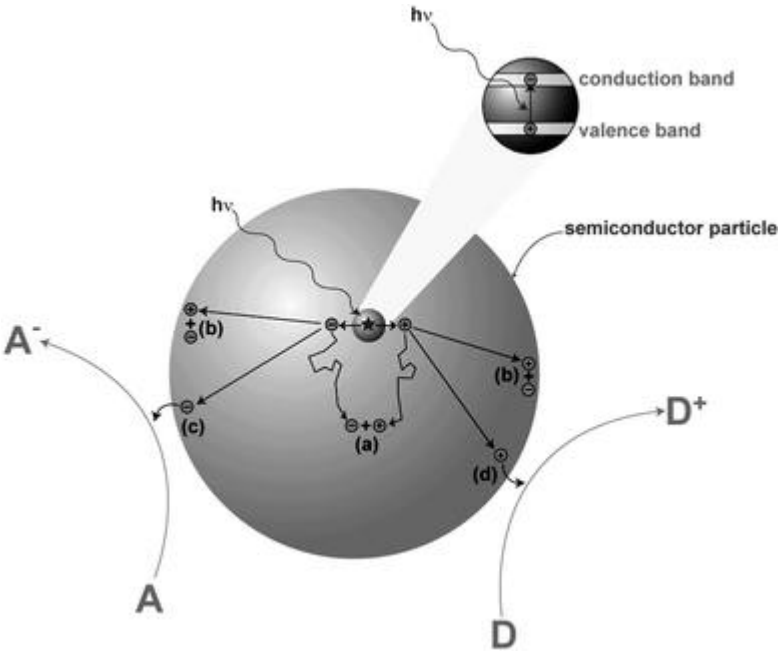


Fig. 5 Photo-excitation processes in TiO_2, leading to redox behaviour. (a) Electron and hole recombination in the bulk, (b) electron

and hole recombination at the surface, (c) adsorbate reduction at the surface and (d) adsorbate oxidation at the surface.

3.3.2.2 Photodisinfection by TiO_2 mediated photocatalysis. Disinfection of a surface by photocatalysed reactions on TiO_2 is a popular possible alternative to using chemical disinfectants such as chlorine bleach because it avoids the use of chemicals for which there are currently concerns about possible toxicity and mutagenesis.[98,102] Consequently, the development of an effective surface activated disinfection system is highly attractive. Researchers are interested as to the mechanism by which titanium dioxide antimicrobial films cause cell death, and this has been a topic of debate since the first work on TiO_2 antimicrobials by Matsunaga *et al.*[89,98] Recently the three competing theories were evaluated[103] and considered in the light of the latest evidence collected. The three theories so far considered are set out below:

1. Direct oxidation of coenzyme A (CoA), which inhibits cell respiration, ultimately leading to cell death. This was the original theory proposed by Matsunaga *et al.*
2. Cell wall decomposition and disorder in cell permeability observed by transmission electron microscopy (TEM).
3. Cell wall damage followed by cytoplasmic membrane damage.

Huang *et al.*[103] considered the above in the light of evidence collected by probing *E. coli* with *ortho*-nitrophenol β-D-galactopyranoside (ONPG). An increase in cell wall permeability to ONPG, and leakage of large molecules from the interior of the cell was observed—reinforcing the third theory above. It was found that damage to the cell wall was non-lethal, whereas breach of the cytoplasmic membrane and leakage of the cytoplasm resulted in cell death. Further corroboratory evidence can be found for this in previous work by Watts *et al.*[102] comparing the efficacy of TiO_2 photodisinfection of viruses and bacteria and by more recent atomic force microscopy (AFM) studies of TiO_2 photodisinfection by Lu *et al.*[104] Watts *et al.*[102] showed that TiO_2 was four times more effective at killing poliovirus 1 than it was at killing common coliform bacteria. The explanation for this lies in the fact that a virus has a much greater surface area to volume ratio than a bacterium, so the rate of surface reactions between the TiO_2 generated hydroxyl radicals and the organic components of the virus is much greater than the equivalent process for a bacterium. Damage is therefore limited to the surface of the microorganism. The latest work in this area by Lu *et al.*[104] examined the effect of TiO_2 on *E. coli*, using AFM and measurement of K^+ ion leakage. AFM was able to demonstrate firstly the decomposition of the cell wall, followed by the destruction of the cell membrane. Cell death was due to leakage of the cytoplasm through the damaged membrane. This was confirmed by a notable increase in K^+ ion concentration leaking from the cells. K^+ ions are vital to bacterial cells as they play a part in protein synthesis—so the detection of a leakage of K^+ ions clearly shows that the cell membrane is compromised by the action of TiO_2 under photocatalytic conditions.

It is perhaps important to note that UV light by itself is known to exert a microbicidal effect due to the ready absorption of light of wavelength less than 300 nm by microbial DNA and the subsequent mutagenesis of these cells.[105] Indeed lamps of 254 nm emission wavelength are commonly referred to as germicidal lamps. This means that one must carefully examine data on photocatalytic inactivation of microbes, to be sure that sufficient controls are included in the experiment design. The controls allow differentiation between the antimicrobial effect of the UV light by itself, or the synergistic action of the UV light and the photocatalyst. This was considered even in the first experiments by Matsunaga *et al.*,[89] where no microbicidal action was observed in the absence of the photocatalyst. However, subsequent studies, such as that of Lu show a small decrease in microbe viability with irradiation.[104] Experiments carried out in our laboratory also show this, but the synergistic effect of ultraviolet illumination, coupled with photocatalyst always produces a superior microbe kill than the UV light by itself.

3.3.2.3 Modifying the TiO_2 surface to increase efficacy. Currently the predominant research area in titania photocatalysis is an exploration of ways in which the material composition can be altered in order to produce films which are either more photocatalytically active, are able to utilise visible light, or both. The effectiveness of the TiO_2 as a photocatalyst is principally dependent upon the rate of production of hydroxyl radicals at the surface of the semiconductor. However, this is in turn dependent upon the energy of the light illuminating the surface and the competition between electron-hole recombination and the redox processes occurring on the surface (see Fig. 5). The ultimate research goal is to synthesise a durable, reusable coating which is more antimicrobially efficient, and which is able to effectively utilise visible light, rather than UV light.

In all research to date the route taken to improve the efficacy of a titania surface is to introduce dopant materials in an attempt to modify the material properties. Often the dopants change the way in which the semiconductor behaves when light (UV or visible) is shone on it. Addition of dopant materials may have three effects:

1. More efficient harvesting of energy from absorbed photons, in effect enabling more energy to be absorbed.

2. Expansion of the wavelength range over which photons can be harvested, so that visible light energy can be used.

3. Maintain separation of charges in the semiconductor, thereby preventing electron-hole recombination and amplifying the photo-redox processes at the catalyst surface.[101]

Although much work has been carried out in the field of semiconductor photocatalysis, the production of visible light activated materials is a comparatively new discipline and is vital in overcoming the dependence of TiO_2 thin films on ultraviolet radiation—the principal disadvantage in using TiO_2 as a LAAA. Visible light activated photocatalysis was reported by Asahi *et al*.[106] in 2001. In this work nitrogen doped titanium oxide ($TiO_{2-x}N_x$) was studied by theoretical simulations, followed by the practical synthesis of the material by sputtering a TiO_2 target in an N_2/Ar atmosphere, followed by annealing in a N_2 atmosphere. The resulting yellowish transparent films demonstrated photocatalytic ability against methylene blue and acetaldehyde. Most interestingly, the UV-Visible spectra of the films show that the nitrogen doping results in a shift of the band edge into the visible light region. It was shown that substitutional doping of N narrowed the band gap due to the mixing of its p states with the 2p on O. The visible light absorbing intra-band gap states formed by this doping are close to the conduction band edge—this allows electronic coupling between the states and the conduction band electrons and prevents electron-hole recombination.[107] Calculations showed that S-doping would have a similar effect, however, the larger ionic radius of S compared with N would make it difficult to incorporate into the TiO_2 crystal.[106] Other dopant materials (fluorine, carbon and phosphorus) were considered, but were deemed unsuitable because the intra-band gap states are located in the centre of the band gap, a situation favouring electron-hole recombination.[106,107]

Another method for narrowing the band gap is to dope the titania with another metal oxide, which has a narrower band gap. One such metal oxide dopant which has already received research interest is WO_3.[108] Tungsten oxide has a band gap of 2.8 eV (equivalent to a light wavelength of 442 nm), which makes the coating able to access the visible solar spectrum, and harvest visible light photons. Inclusion of another metal oxide semiconductor, such as WO_3, also provides an enhancement in charge separation, by preventing the recombination of electrons and holes.[109] These combined effects allow the surface to be more photocatalytically active and more superhydrophilic than an anatase control. This effect was demonstrated by Rampaul *et al*.[108] with a 2% loading of WO_3/TiO_2.

Coatings such as those described above may have the potential to be highly successful antimicrobial coatings due to the combined effects of narrower band gap, greater photocatalytic ability and surface superhydrophilicity. In effect they would be self-disinfecting (*via* photocatalysis) and easy to clean (due to surface superhydrophilicity) even under visible light because of the narrower band gap. Visible light activated photocatalysts are likely to become the principal focus for semiconductor photocatalysis research because of the potential real world

use and importance of these new materials.

4. Conclusion

Hospital acquired infections are a significant health concern in developed countries. Microbes such as MRSA and *C. difficile* have been implicated with a large number of deaths as well as enormous additional healthcare costs. The growing resistance of microbes to antibiotics is a significant cause for concern. This has prompted improved cleaning protocols within hospitals. Despite this, HAIs have not been, and probably never will be, completely eradicated. The development of surfaces and coatings that can actively kill microbes is an important component of maintaining a microbially-clean environment and a wide number of methods have been developed. Ideally these antimicrobial surfaces should be permanent, hard-wearing and work under hospital conditions. The mode of action in killing microbes needs to function simultaneously through multiple pathways, so that the development of resistance, as seen for antibiotics and diffusible antimicrobials, is avoided. In that context, the light-activated antimicrobials offer particular promise as they function by generating reactive oxygen species that act on multiple targets within microbes. Furthermore, titanium dioxide coatings offer both reactive oxygen species and a superhydrophilic surface that is both easy to clean and hard for a microbe to adhere to. Surprisingly, one straightforward way to help eliminate microbial spread is to use copper or copper based metals such as brass within a hospital. It would be relatively straightforward for steel push plates on hospital doors to be replaced with brass. These brass plates have been demonstrated to have potent microbicidal properties.

The current widespread armoury of antimicrobial coatings gives hope for reducing hospital-acquired infections. However, these coatings, without a strict hygiene regime, will have limited benefit.

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