Photocatalytic antimicrobial coatings

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Abstract

The application of photocatalytic antimicrobial coatings (PAC) to diminish the occurrence of healthcare-associated infections (HAI) is critically evaluated. There is little doubt that PAC have a microbiocidal action and, hence, must reduce the environmental burden of microbes wherever PAC are deployed, but the link thence to reducing HAI is not straightforward and needs to be carefully examined in order to ensure that PAC are deployed cost-effectively. The likely mechanism of the microbicidal action is examined, especially with respect to the possible development of resistance. The relative merits of nanoparticulate versus monolithic films are discussed, as well as the choice of catalyst. Titanium dioxide is the preferred material, but suffers from the small overlap of its optical absorption with the visible spectrum. Efforts to increase the degree of visible light activation of catalysis are surveyed. The overall goal of this article is to provide the scientific and technical basis for the effectiveness of PAC in order to serve as a guide to appropriate decisions within healthcare environments.

Contents

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1. Introduction

Hospitals are by definition places where congeries of ill people are gathered, including those suffering from infectious diseases. Hence, there is inevitably a higher concentration of the infectious agents (microbes, i.e. chiefly viruses, bacteria and fungi) present than in the community outside. This gives rise to the very real, as well as expensive and demoralizing, occurrence of hospital-acquired (or nosocomial) infection.

The problem of hospital-acquired infection (HAI) is now compounded by the rise of antimicrobial resistance to antibiotics. Since the discovery of the category of substances known as antibiotics by Alexander Fleming in the 1920s, they have been the main weapon to combat microbial infection. It is instructive to recall the environment in which the discovery was made. Fleming and his mentor Almroth Wright served as military doctors during the First World War, during which immense experience in treating wounds was accumulated. Prior to the war, the surgeon's goal in treating a wound was asepsis (i.e., exclusion of microbes). Under war pressures, the careful dressing required could not always be achieved, hence the *antiseptic school* of practice arose, which aimed at killing the microbes in the wound with some chemical agent.[1] It was opposed by the *physiological school*, favoured by Wright, which aimed at helping the natural protective agencies of the body (blood and tissue fluids, and leucocytes) against infection. Fleming showed that the leucocytes are more susceptible to the action of chemical antiseptics than are the bacteria. Moreover, he showed that the demonstrable efficacity of the antiseptics against bacteria in aqueous solution greatly exaggerates the state of affairs under normal physiological conditions: the presence of blood, tissue fluids and tissue greatly attenuates the bactericidal power of the antiseptics. In fact, as the concentration of the antiseptic carbolic acid (phenol) is increased from zero, the growth of *B. welchii* in serum is actually promoted, and only at concentrations above 0.125% (which is much too concentrated to be used in practice) does the growth start to diminish.[1] The explanation of this result is that initially it is the antibacterial leucocytes that are killed by the phenol.

Since Fleming's discovery of penicillin, the first antibiotic, many different classes of antibiotics have been discovered; some of them, like penicillin, extracted from organisms and others synthesized in the laboratory. Hospitals, inevitably, have become loci of the intensive deployment of antibiotics. This, in turn, imposes intense selection pressure on the microorganisms, which generally have the capacity to deploy or evolve resistance mechanisms.[2] Almost inevitably, and for a variety of reasons, exposure to antibiotics is heterogeneous, which offers particularly favourable circumstances for the rapid acquisition of resistance by a heterogeneous population.[3, 4] In countries like India, which have a large indigenous pharmaceutical industry manufacturing generic antibiotics, they are so widely

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[1] A. Fleming, The action of chemical and physiological antiseptics in a septic wound (Hunterian Lecture). *Br. J. Surgery* **7** (1919) 99–129.

[2] J. Vohradský and J.J. Ramsden, Genome resource utilization during procaryotic development. *FASEB J.* **15** (2001) 2054–2056.

[3] T.B. Kepler and A.S. Perelson, Drug concentration heterogeneity facilitates the evolution of drug resistance. *Proc. Natl Acad. Sci. USA* **95** (1998) 11514–11519.

[4] R. Hermsen et al., On the rapidity of antibiotic resistance evolution facilitated by a concentration gradient. *Proc. Natl Acad. Sci. USA* **109** (2012) 10775–10780.

available that they may be purchased over-the-counter by the general population without a doctor's prescription, hence contributing to the spread of antibiotic resistance in the community. Within hospitals, the prevalence of resistant microbes has reached alarming proportions in some countries.[5] The rapid, seemingly exponential, growth of resistance in recent years has led to the gravest concerns being expressed by public health officials,[6] who fear that antibiotics may soon be powerless to tackle infection.

This state of affairs has, essentially, caused a reversion to the era preceding that of antibiotics. If they are no longer effective, other means must be found to keep microorganisms under control. Within the community of hospital hygienists, there is great controversy regarding the source of the (pathogenic) microorganisms, antibiotic-resistant or otherwise. The two extremes of the spectrum of viewpoints can be represented as follows. According to the "organism" viewpoint, the patient is himself or herself the source of the microbes that infect the vulnerable sites, such as a postsurgical wound or an implant.[7] According to the "environment" viewpoint, the fabric of the hospital, including furniture and medical devices, constitutes a reservoir of (pathogenic) microbes (which must have, of course, originally been released from a carrying organism), which then supplies the pathogens to the vulnerable sites. The evidence for these viewpoints is reviewed in Sections 2 and 3. The balance of importance between them has profound implications for infection management policies in hospitals.

2. The organism as a source of infectious agents

The initially inspiring, but ultimately tragic story of Ignaz Semmelweis is too well known to require retelling in any detail. There were two clinics for childbirth in the Vienna General Hospital where he worked. In one, the mothers were attended to by midwives; in the other by the medical doctors of the hospital. Semmelweis observed that the death rate from puerperal fever in the clinic for mothers attended to by the medical doctors and students was about 16%, compared with about 2% in the other. He hypothesized that the difference was due to the medical doctors frequently examining the mothers after coming straight from the mortuary, where they had been examining cadavers. In order to test this hypothesis, he instituted a strict régime of hand-washing in a chlorine-based disinfectant (calcium hypochlorite[9]) for the

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5 *Antimicrobial Resistance: Global Report on Surveillance*. Geneva: World Health Organization (WHO) (2014); *Worldwide Country Situation Analysis: Response to Antimicrobial Resistance*. Geneva: *idem* (2015).

6 J. O'Neill, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*. London: HM Government & Wellcome Trust (2014).

7 "The major source of healthcare-associated pathogens is thought to be the patient's endogenous flora, but an estimated 20% of pathogens are acquired by other transmission routes, such as the environment, and 20%–40% is attributed to cross-infection via the contaminated hands of healthcare personnel".[8]

8 S.J. Harbarth et al., The environment and health-care-acquired infections: why accurate reporting and evaluation of biological plausibility are important. *Infection Control Hospital Epidemiol.* **34** (2013) 996–997; C.D. Salgado et al., Reply to Harbarth et al. *Infection Control Hospital Epidemiol.* **34** (2013) 997–999.

9 Many hand-hygiene agents are nowadays available. See, for example, E.E. Sickbert-Bennett et al., Comparative efficacy of hand hygiene agents in the reduction of bacteria and viruses. *Am. J. Infection Control* **33** (2005) 67–77.

medical doctors before they entered the clinic. The death rate promptly fell to the same rate as that in the other clinic. After a further régime of washing the medical instruments was instituted, the death rate fell to about 1%.[10]

We shall pass over the strenuous resistance of most of the doctors to the innovation. Clearly this kind of source of pathogenic microbes can be blocked straightforwardly by insisting on hand-washing. Nevertheless, there seems to be a practical limit to the amount of hand-washing achievable. 150 years after Semmelweis, the principle is generally accepted and has become part of our culture, even well beyond the healthcare environment. Despite this, the degree of compliance (e.g., with the rule that hands must be washed after every patient contact) is still far from 100% (such statistics as are available show a wide range).[11] Hospital hygienists have devised ingenious strategies in an attempt to increase the degree of compliance, such as equipping hand-washing locations, and even faucets, with sensors able to monitor hand-washing activity. Some hospitals even continuously track the movements of all individual healthcare workers.[12] Such intensive surveillance, however, evokes hostility and may end up being counterproductive. "Waschzwang"—compulsive hand-washing—is indeed recognized as a kind of psychiatric disorder. Given the universality of knowledge of Shakespeare, typically acquired during impressionable school years, Lady Macbeth's "Out, damned spot! out, I say! ... What, will these hands ne'er be clean?" doubtless remains in the memory as a symptom of an advanced stage of this disorder which, ultimately, proved to be fatal in her case.

Furthermore, even the strictest hand-washing discipline applied to medical staff cannot prevent the transmission of infectious agents from the patient as carrier to his or her own wounds. The danger of such transmission is, again, a peculiar circumstance of the hospital. For example, *Escherichia coli* is a vital part of the flora of the human intestine, but should it be transmitted to a catheter in the urinary tract, it may engender severe inflammation.[13]

3. The environment as a source of infectious agents

Since we no longer believe in the spontaneous generation of life, an organism is still the ultimate source. The difference between the "organism" viewpoint (Section 2) and the "environmental" viewpoint is that in the former, transmission is assumed to occur by direct

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[10] Contamination of medical instruments has recently been the subject of renewed interest. See, e.g., W.A. Rutala et al., Levels of microbial contamination on surgical instruments. *Am. J. Infection Control* **26** (1998) 143–145; Y. Longtin et al., Contamination of stethoscopes and physicians' hands after a physical examination. *Mayo Clinic Proc.* **89** (2014) 291–299.

[11] D. Pittet, Improving compliance with hand hygiene in hospitals. *Infection Control Hospital Epidemiol.* **21** (2000) 381–386; *idem*, Improving adherence to hand hygiene practice: a multidisciplinary approach. *Emerging Infectious Diseases* **7** (2001) 234–240.

[12] For example, the "CenTrak" system installed at New Cross Hospital, Wolverhampton, England in 2014 as part of its "SafeHands" programme.

[13] Cf. J. Peter et al., Incidence and clinical implication of nosocomial infections associated with implantable biomaterials—catheters, ventilator-associated pneumonia, urinary tract infections. *GMS Krankenhaushygiene Interdisziplinär* **6** (2011) issue no 1 (19 pp.)—online only. PAC have been advocated for coating catheters, in order to provide a convenient means of sterilizing them prior to use: see Y. Sekiguchi et al., Self-sterilizing catheters with titanium dioxide photocatalytic thin-films for clean intermittent catheterization: Basis and study of clinical use. *Intl J. Urol.* **14** (2007) 426–430.

contact between the carrier and the receiver, whereas in the latter the carrier disseminates his, her or its microorganisms into the environment, from which they are later on picked up by the recipient (Figure 1).

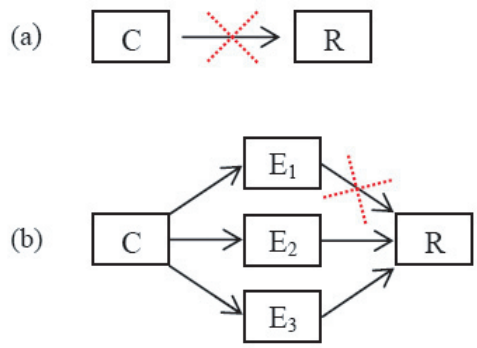

Figure 1. (a) The organism as the source and carrier (C) of infectious agents, whence they are directly transmitted to the recipient (R). (b) The organism (carrier) as the remote source, but the environment (E) as the proximate source of infectious agents transmitted to R. Hypothetical blockage of a transmission channel is indicated by the dotted grey (red online) "X".

An immediate implication of the "environment" model is that the infectious agents can be fanned out to many diverse environments, from each of which they might be picked up by the recipient. Hence, it is very difficult to completely block transmission. On the other hand, with the organism model, a single rigorously applied measure (such as Semmelweis' hand-washing) should suffice to block transmission (except for transmission of the patient's own microorganisms to his or her wound).

Microorganisms are, obviously, likely to be found on the hands of healthcare workers (HCW) who have been examining patients. In diagram (b) of Figure 1, E_1 could be considered to be a composite unit comprising the HCW's hands, which first receive the microorganisms from C, and which then transfer them to the ubiquitous touch surfaces such as door handles, computer keyboards, control knobs on instruments, and writing implements.[14, 15]

It is also known that any human being continually releases clouds of microorganisms into the air.[16] Ultimately they will collide with any kind of surface, with a certain probability of sticking, which can be directly related to the interfacial interaction energy between the microorganism and the particular surface. Referring again to diagram (b) of Figure 1, E_2 could be considered as a composite unit comprising the air and solid surfaces.

Although, according to a theorem due to Pólya, in three dimensions a simple random walk is transient, but recurrent in one and two dimensions (i.e., a randomly diffusing particle

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[14] J.M. Boyce et al., Environmental contamination due to methicillin-resistant *Staphylococcus aureus*: Possible infection control implications. *Infection Control Hospital Epidemiol.* **18** (1997) 622–627.
[15] S.J. Smith et al., Where do hands go? An audit of sequential hand-touch events on a hospital ward. *J. Hospital Infection* **80** (2012) 206–211.
[16] J.F. Meadow et al., Humans differ in their personal microbial cloud. *Peer J.* **3** (2015) e1258.

will, in infinite time, return infinitely often to any point in one and two dimensions, but not in three),[17] the airborne transmission of microorganisms onto inanimate surfaces is considered to be significant.[18–20]

Nevertheless, in 1999 Talon could remark "There is as yet no direct proof that the environment acts as a secondary reservoir for the infection of patients with multiresistant bacteria in epidemics or endemic situations. However, there is now sufficient indirect evidence to suggest that this is highly likely. Unfortunately, some of the measures intuitively developed to control environmental reservoirs of multiresistant bacteria have not been rigorously evaluated as part of an overall strategy to prevent infections".[21] Neely and Maley showed that Gram-positive bacteria could survive for a significant length of time on hospital fabrics and polymer surfaces.[22] Bures et al. showed that computer keyboards and faucet handles were reservoirs of microbial pathogens in an intensive care unit,[23] similar work with respect to door handles being done by Oie et al.[24] In 2001 Rutala and Weber recommended the regular cleaning and disinfection of surfaces, even though they concluded that "noncritical surfaces are uncommonly associated with transmission of infection to patients".[25] This somewhat illogical recommendation was criticized by Rüden and Daschner, who pointed out that such studies as had been done suggested that "microorganisms in the inanimate hospital environment—particularly in surfaces and in the air—contribute negligibly to endemic rates of hospital-acquired infection";[26(a)] Hota suggested that the

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[17] G. Pólya, Ueber eine Aufgabe der Wahrscheinlichkeitsrechnung betreffend die Irrfahrt im Strassennetz. *Math. Ann.* **84** (1921) 149–160. The escape probability in three dimensions is about one third (E.W. Montroll, Random walks in multidimensional spaces, especially on periodic lattices. *J. Soc. Ind. Appl. Math.* **4** (1956) 241–260).

[18] T. Shiomari et al., Significance of airborne transmission of methicillin-resistant *Staphylococcus aureus* in an otolaryngology–head and neck surgery unit. *Arch. Otolaryngol. Head Neck Surgery* **127** (2001) 644–648.

[19] C.B. Beggs, The airborne transmission of infection in hospital buildings: fact or fiction? *Indoor Built Environ.* **12** (2003) 9–18.

[20] Y. Li et al., Role of ventilation in airborne transmission of infectious agents in the built environment—a multidisciplinary systematic review. *Indoor Air* **17** (2007) 2–18.

[21] D. Talon, The role of the hospital environment in the epidemiology of multi-resistant bacteria. *J. Hospital Infection* **43** (1999) 13–17.

[22] A.N. Neely and M.P. Maley, Survival of enterococci and staphylococci on hospital fabrics and plastic. *J. Clin. Microbiol.* **38** (2000) 724–726.

[23] S. Bures et al., Computer keyboards and faucet handles as reservoirs of nosocomial pathogens in the intensive care unit. *Am. J. Infection Control* **28** (2000) 465–470.

[24] S. Oie et al., Contamination of room door handles by methicillin-sensitive/methicillin-resistant *Staphylococcus aureus*. *J. Hospital Infection* **51** (2002) 140–143.

[25] W.A. Rutala and D.J. Weber, Surface disinfection: should we do it? *J. Hospital Infection* **48** (Supplement A) (2001) S64–S68. The message of this paper was further reinforced in *idem*, The benefits of surface disinfection. *Am. J. Infection Control* **32** (2004) 226–231.

[26] (a) H. Rüden and F. Daschner, Should we routinely disinfect floors? *J. Hospital Infection* **51** (2002) 309. See the reply by Rutala and Weber, *J. Hospital Infection* **51** (2002) 309–311. The critique of surface disinfection was continued in Dettenkofer et al., Does disinfection of environmental surfaces influence nosocomial infection rates? A systematic review. *Am. J. Infection Control* **32** (2004) 84–89. (b) M. Dettenkofer and R.C. Spencer, Importance of environmental decontamination—a critical view. *J. Hospital Infection* 65 Suppl 2 (2007) 55–57.

evidence for cross-colonization is indirect.[27] Furthermore, Rüden and Daschner pointed out that allergy to disinfectants is a major occupational disease amongst nurses and cleaning staff.

A summary of the positions was offered by Dettenkofer and Spencer,[26(b)] who pointed out that "targeted disinfection of environmental surfaces (those frequently touched) is an established component of infection control activities to prevent the spread of nosocomial (multi-resistant) pathogens, but of lesser importance than proper hand hygiene" and pointed out that "well-designed studies addressing the role of disinfection in the healthcare setting are needed". The emphasis on hand-touch surfaces, rather than floors, was reinforced in the review by Dancer,[28] who also sagely pointed out that "Introduction of additional cleaning services is easier than improvements in hand-hygiene compliance". Further evidence for bacterial contamination of hand-touch surfaces was provided by Otter and French.[29]

4. Strategies to diminish the environmental burden of microorganisms

4.1 *Touch surfaces*

The traditional strategy to arrest environmentally-mediated contamination was to fabricate the touched artefacts from a microbicidal material. Copper and silver are effective in this regard, and have long been used for door handles and the like, as well as for coins circulating publicly (for which the microbicidal attribute may be an exaptation, but at any rate it is doubtless very useful). Pure silver is too soft for many applications, and even the harder copper has often been alloyed (e.g., with tin to make bronze or with zinc to make brass) for artefacts requiring a certain mechanical strength.

A recent study in which some frequently touched objects in intensive care units were replaced with equivalents fabricated from a variety of solid copper alloys purported to show that healthcare-associated infection in the units was reduced by more than half.[30] Doubts as to the validity of that conclusion were raised, not least because of the biological implausibility of the result.[8] Besides, in comparison with the usual materials such as polymers, copper and silver are regarded as being comparatively too expensive—both the material itself and the shaping required to make the final object—for what has become probably the most ubiquitous type of touch surface: computer keyboards and other buttons, knobs, and switches (the Salgado et al. study[30] also included copper bed rails and chair arms, etc.). Hence, interest has grown in applying microbicidal *surface coatings*.[31] This has a number of advantages: the microbicidal action can be developed independently from mechanical strength and other attributes (although it should not be soft, otherwise it will be rapidly worn away); because the amount of material is

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[27] B. Hota, Contamination, disinfection, and cross-colonization: are hospital surfaces reservoirs for nosocomial infection? *Clin. Infectious Diseases* **39** (2004) 1182–1189.

[28] S.J. Dancer, Importance of the environment in meticillin-resistant *Staphylococcus aureus* acquisition: the case for hospital cleaning. *Lancet Infectious Diseases* **8** (2008) 101–113.

[29] J.A. Otter and G.L. French, Bacterial contamination on touch surfaces in the public transport system and in public areas of a hospital in London. *Lett. Appl. Microbiol.* **49** (2009) 803–805.

[30] C.D. Salgado et al., Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. *Infection Control Hospital Epidemiol.* **34** (2013) 479–486.

[31] K. Page et al., Antimicrobial surfaces and their potential in reducing the role of the inanimate environment in the incidence of hospital-acquired infections. *J. Mater. Chem.* **19** (2009) 3819–3831.

small, even costly substances can be deployed; and artefacts can be retroactively treated, post-manufacture. If the object is not too large and can be placed in a vacuum chamber, sputtering or evaporation could be used to apply a coating post-manufacture, otherwise painting or spraying is required. Copper and silver can be prepared in the form of suspended nanoparticles suitable for painting or spraying.[32]

These metals are not, however, ideal because they are also toxic to humans. Some microbicidal metals such as nickel are allergenic. Furthermore, the antimicrobial action requires the uptake of the metal (ions) by the microbes, hence the material is gradually consumed (apart from loss through abrasion; i.e., repeated touching). Hence there is interest in finding materials that catalyse the decomposition of microbes. No such catalyst is currently known, and were one to be discovered or invented, it would likely be too reactive to be practically useful: it might be dangerous to touch, and might become rapidly poisoned from the adsorption of aerial contaminants. An ingenious way to overcome those disadvantages is to use a *photo*catalytic material: light, which is usually available in abundance, provides the energy to break the chemical bonds, such breakage being implicit in any scheme of microbial destruction. Photocatalytic materials will be discussed in detail in Section 5. It may already be remarked that among the range of available materials are not many that are nontoxic to humans, inexpensive and durable.

Other kinds of antimicrobial coatings have also been explored. Insofar as the effects of copper and silver are due to the release of the corresponding metal ions and their uptake by the microbes,[33] coatings that contain, and slowly release, an antibiotic such as rifampicin or a biocide such as triclosan belong to the same category. Silver ions can be dispersed in a polymer to achieve a similar effect.[34] A further variant is silver zeolite.[35] Alkyl-substituted quaternary amines also have an antibacterial effect.[36] Such materials releasing the microbicide from a reservoir are generally only useful for short-term deployment, for example on temporary implants. It is sobering to know that a silicone quaternary amine antimicrobial surface polymer had no significant effect on environmental contamination in a hospital setting.[37] Some novel block copolymers appear to act antimicrobially by a contact effect,[38] which should make them longer-lasting; it has been hypothesized that polycation moieties can penetrate and disrupt bacterial cell walls,[39] which makes such polymers in effect catalytic.

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[32] N. Cioffi and M. Rai (eds), *Nano-Antimicrobials*. Heidelberg: Springer (2012).

[33] Silver nanoparticles may be taken up in their entirety by cells and release silver ions once inside (E.-J. Park et al., Silver nanoparticles induced cytotoxicity by a Trojan-horse type mechanism. *Toxicology In Vitro* **24** (2010) 872–878).

[34] C.H. Ho et al., Nano separated polymeric networks with multiple antimicrobial properties. *Adv. Mater.* **16** (2004) 957–961.

[35] Y. Matsumura et al., Mode of bactericidal action of silver zeolite and its comparison with that of silver nitrate. *Appl. Environ. Microbiol.* **69** (2003) 4278–4281.

[36] J.C. Tiller et al., Amphiphilic conetworks as regenerative controlled releasing antimicrobial agents. *J. Controlled Release* **103** (2005) 355–367.

[37] K.A. Thom et al., Effectiveness of an antimicrobial polymer to decrease contamination of environmental surfaces in the clinical setting. *Infection Control Hospital Epidemiol.* **35** (2014) 1060–1062.

[38] A.D. Fuchs and J.C. Tiller, Contact-active antimicrobial coatings derived from aqueous suspensions. *Angew. Chem. Intl Edn* **45** (2006) 6759–6762.

[39] J.C. Tiller et al., Designing surfaces that kill bacteria on contact. *Proc. Natl Acad. Sci. USA* **98** (2001) 5981–5985.

Conventional cleaning. If it is not possible to render the touch surfaces adequately microbicidal, then they must be regularly cleaned by the application of disinfectant, usually in liquid form. Rutala and Weber have summarized the attributes of an ideal disinfectant,[40] which include a broad antimicrobial spectrum, fast action, nonirritating and nontoxic, surface compatible, economical and so forth. No commercially available product fulfils all these criteria. Regardless of how good they are *per se* (i.e. as microbicides), all disinfectants suffer from the following disadvantages:

1. The need for repeated applications. In some cases the objects being disinfected must be taken out of service during the disinfection procedure.

2. Item 1 implies the expenses of materials and labour.

3. Because of their toxicity and allergenicity, they must be removed from the surfaces after they have been allowed to act for a certain time. From then until the next cleaning, the surfaces start to become contaminated again.[41]

4. The chemicals are generally indiscriminately harmful to benign microbes, hence special and expensive procedures are required to dispose of used disinfectant.

5. There is always a risk that some critical surface might be missed.

Conventional and some new cleaning technologies are extensively described by Dancer.[42] That a disinfectant was no better than a simple detergent for lowering the environmental microbial burden[43] nor, indeed, than no cleaning at all,[44] are sobering facts for consideration.

4.2 *The atmosphere*

Given the undoubted existence of airborne pathogens, continuously sucking the air through appropriate filters using powerful fans should somewhat contribute to hospital hygiene. On a small scale, microbiological work is conducted in special cabinets in which sterile air is continuously circulated and filtered to minimize cross-contamination. Upscaling this principle is, however, rarely if ever done. The resulting noise and draughts would be inconvenient and worse. Furthermore, it does not seem possible to achieve complete sterility by this means; hence, some auxiliary cleaning of surfaces would always be necessary.

Many modern buildings are, however, designed to rely on forced ventilation by being equipped with comprehensive air-conditioning systems. While the efficiency of circulation within the interior rooms is rarely as good as in, say, the interior of a pressurized airliner cabin it offers a compromise between essentially being in a wind tunnel and stagnant air. As well as filtration (typically using "high-efficiency particle-arresting", HEPA, filters), ultraviolet light is

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[40] W.A. Rutala and D.J. Weber, Selection of the ideal disinfectant. *Infection Control Hospital Epidemiol.* **35** (2014) 855–865.

[41] A. Bogusz et al., How quickly do hospital surfaces become contaminated after detergent cleaning? *Healthcare Infection* **18** (2013) 3–9.

[42] S.J. Dancer, Controlling hospital-acquired infection: focus on the role of the environment and new technologies for decontamination. *Clin. Microbiol. Rev.* **27** (2014) 665–689.

[43] D. Danforth et al., Nosocomial infections on nursing units with floors cleaned with a disinfectant compared with detergent. *J. Hospital Infection* **10** (1987) 229–235.

[44] G.A.J. Ayliffe et al., Ward floors and other surfaces as reservoirs of hospital infection. *J. Hygiene* (Camb.) **65** (1967) 515–536 (with one plate facing p. 536).

often employed to sterilize the air. Low-pressure mercury lamps emit light mainly at 253.7 nm (within the range called UV-C), which is germicidal (DNA-destroying) and at 184.9 nm, which is absorbed by oxygen, generating ozone. The combination of UV-C and ozone appears to act synergistically to enhance cleaning and sterilization.[45] Since ozone is toxic to humans it must be removed from the air before humans re-enter the room. Photocatalysis using longer-wavelength UV light (380 nm) has also been proposed and demonstrated for sterilization.[46]

The generation of ozone prevents 184.9 nm ultraviolet light from being used directly in spaces occupied by humans. "Germicidal" UV-C (such as 253.7 nm) is, however, effective in disinfecting rooms even with a short (~10 min) exposure.[47] It has recently been demonstrated that violet–blue light (405 nm), which does not generate ozone from oxygen, is able to continuously disinfect air and exposed surfaces;[48] the authors of this review only view it as a means to enhance conventional cleaning and infection control procedures, however, not to replace them.

4.3 *Nontouch surfaces*

Little work seems to have been done to investigate where microbes released into the atmosphere from humans walking around end up. Insofar as all microbes are denser than air, and probably no microbe sticks permanently to any surface, their ultimate destination must be the floor (notwithstanding Pólya's recurrence theorem[17]). Although most hospitals do indeed regularly clean their floors, the practice is controversial insofar as there is little if any empirical evidence for its efficacity in diminishing hospital-acquired infection rates.[26] Anecdotally it might even be harmful: some decades ago it was accepted practice for surgeons to keep their street shoes on in the operating theatre, on the premiss that they thereby brought in generally harmless environmental microbes that would outcompete the harmful (pathogenic and antimicrobial-resistant) ones. Ayliffe et al. found that about half the bacterial contamination of floors comes from the air, and about half from the soles of shoes and the wheels of mobile furniture.[44] Given the constant traffic of people in a hospital, many of whom are pushing mobile furniture, it is hardly surprising that daily cleaning (i.e., once every 24 hours), whether with disinfectant or simple detergent, does not significantly change the microbial burden.

From the cybernetic viewpoint, the floor is an absorbing state (Figure 2), differing in this regard from the walls and ceilings because of gravity. Shoes bring a constant supply of microbes from the exterior of the hospital. Shoes also pick up microbes from the floor. In this regard it may be pertinent to note very different national customs regarding where shoes may and may not be placed. For example, in England it appears to be unexceptionable to place them on upholstered seats; in Japan they are normally removed at the entrances to buildings. Presumably this affects the dissemination of microbes, although whether significantly does not appear to have ever been investigated.

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[45] J.R. Vig, UV/ozone cleaning of surfaces. *J. Vac. Sci. Technol. A* **3** (1985) 1027–1034.

[46] V. Keller et al., Biological agent inactivation in a flowing air stream by photocatalysis. *Chem. Commun.* **23** (2005) 2918–2920.

[47] W.A. Rutala et al., Room decontamination using an ultraviolet-C device with short ultraviolet exposure time. *Infection Control Hospital Epidemiol.* **35** (2014) 1070–1072.

[48] M. Maclean et al., 405 nm light technology for the inactivation of pathogens and its potential role for environmental disinfection and infection control. *J. Hospital Infection* **88** (2014) 1–11.

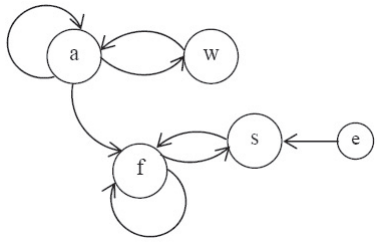

Figure 2. Kinematic graph of the microbial burden of a hospital (partial representation). The states are: a, air; e, external environment; f, floors; s, shoes and wheels; w, walls and ceilings. The re-entrant arrow attached to a represents the escape probability of a random walker in three dimensions.[17] The absence of the re-entrant arrow attached to w signifies that isolated microbes on an essentially clean surface will eventually die.

Figure 2 should be complemented by Figure 3, extending the kinematic graph to people and touch surfaces. In this part of the graph, there is no absorbing state. Hence, the floor is the ultimate repository, which makes it easy to understand why floor cleaning has so little effect.[44, 43] One might then well ask, what would be the result if the floors were *never* cleaned? Presumably there would be a gradual accumulation of ever-larger pieces of debris; floors might become slippery or sticky from accidentally dropped liquids (e.g., beverages), which could also serve to supply nutrients to bacteria and fungi; but ultimately some kind of equilibrium would be achieved (because of the constant traffic). Larger pieces of debris might be a nuisance (e.g., they might get caught in the wheels of mobile furniture, jamming them). There is also the psychological aspect ("litter begets litter", although this seems to lack the supporting evidence of a controlled trial) which, if substantiated, implies that the accumulation of debris would forever increase exponentially.

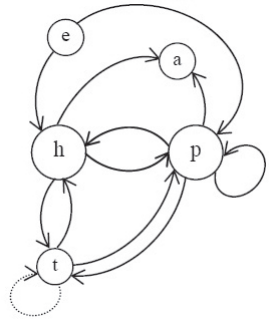

Figure 3. Kinematic graph of that part of the microbial burden involving humans. The states are: a, air (this state should be superimposed on a in Figure 2); e, external environment; h, healthcare workers; p, patients; t, touch surfaces. The re-entrant arrow attached to p represents the transmission of the patient's indigenous microbes to his or her wounds. The dotted re-entrant arrow attached to t signifies that little is known about the survival of microbes on touch surfaces. For simplicity, visitors are omitted.

4.4 *Discharge, terminal and "deep" cleaning*

Some form of cleaning of the space used to accommodate a patient is generally undertaken when the patient leaves that space. The intensity of cleaning depends on knowledge of the infectious burden of the patient, strongly tempered by practical considerations.

Thus, the infectious status of a patient or hospital visitor waiting on a chair in a corridor or waiting-room is unlikely to be known and no cleaning is likely to be carried out when the seated person gets up and leaves.

After a journey ferrying a patient, an ambulance might be cleaned with a dustpan and brush to remove any obvious debris. Most patients carried by ambulances are suffering from an acute injury rather than an infectious disease, hence such light cleaning may well be adequate.

Similarly, if a room in a ward has been occupied by a patient not known to be suffering from any dangerous pathogenic infection, upon discharge a rapid (probably taking less than 10 min) process of light cleaning is undertaken ("discharge cleaning").

If an area has been occupied by a patient known to be suffering from an infection ("alert organism" or communicable disease), more thorough (first with detergent, then with disinfectant)[49] "terminal cleaning" is carried out after the departure (discharge or transfer) of the patient. Bed screens, curtains and bedding are removed prior to decontamination, which then proceeds from the highest (curtain rails) to the lowest (floors), and from the least contaminated (infrequently touched) surfaces to the most. The efficiency of cleaning appears to be significantly affected by ritualistic aspects[50] (i.e., ritual not risk assessment determines what gets cleaned, and how thoroughly).

Outbreaks of alert organisms or communicable disease generally necessitate more thorough cleaning called deep cleaning. In essence it is the extension of terminal cleaning to encompass much more than the area occupied by a single patient. In extreme cases it might encompass the entire establishment. Hydrogen peroxide vapour (HPV) has become a popular instrument of deep cleaning.[51, 52] Commercially available robots are often used to carry out the decontamination but insofar as they are programmed by human beings, they suffer from the same ritualistic limitations as human cleaners. HPV has been shown to be more effective than UV-C.[53] A more comprehensive study showed that traditional chlorine-releasing disinfectants are as effective as modern methods.[54, 55]

5. Photocatalytic materials

Photocatalytic materials are semiconductors. Incident light of an energy exceeding that of the band gap excites an electron from the valence band (VB, Figure 4) into the conduction band (CB) leaving a "positive hole" or "defect electron" in the valence band. If these two charge

[49] This appears to be general practice, even though the evidence for the superiority of decontamination by disinfectant over detergent alone is not particularly convincing. See, e.g., M.H. Wilcox et al., Comparison of the effect of detergent versus hypochlorite cleaning on environmental contamination and incidence of *Clostridium difficile* infection. *J. Hospital Infection* **54** (2003) 109–114.

[50] J.M. Boyce et al., Variations in hospital daily cleaning practices. *Infection Control Hospital Epidemiol.* **31** (2010) 99–101.

[51] G.L. French et al., Tackling contamination of the hospital environment by methicillin-resistant *Staphylococcus aureus* (MRSA): a comparison between conventional terminal cleaning and hydrogen peroxide vapour decontamination. *J. Hospital Infection* **57** (2004) 31–37.

[52] H.-T. Chan et al., Evaluation of the biological efficacy of hydrogen peroxide vapour decontamination in wards of an Australian hospital. *J. Hospital Infection* **79** (2011) 125–128.

[53] N.L. Havill et al., Comparison of the microbiological efficacy of hydrogen peroxide vapor and ultraviolet light processes for room decontamination. *Infection Control Hospital Epidemiol.* **33** (2012) 507–512.

[54] L. Doan et al., Clinical and cost effectiveness of 8 disinfection methods for terminal disinfection of hospital isolation rooms contaminated with *Clostridium difficile* 027. *J. Hospital Infection* **82** (2012) 114–121.

[55] HPV cleaning involves filling the room with hydrogen peroxide vapour, waiting some time for it to act, and then clearing it from the room. Considering that this procedure is already used quite widely, it has been subject to relatively little scrutiny. Simple diffusion would be far too slow to ensure penetration of the vapour into all the nooks and crannies of the room being treated, hence the vapour is delivered in the form of a powerful jet (because of the toxicity of HPV, the procedure is carried out by a remotely controlled robot). Even so, baffles such as partitions and furniture are likely to prevent all surfaces from being uniformly disinfected. Hydrogen peroxide is not particularly expensive; the main cost of deep cleaning is due to the rooms being treated being taken out of healthcare service for many hours.

carriers are not promptly separated, they will rapidly recombine (i.e., the electron falls back into the positive hole). In bulk materials charge separation is achieved by band-bending at the surface of the material (Figure 4). Most commonly the electric field generated in the near-surface depletion layer (space charge) is of a sign such that the positive holes are swept to the surface and the electrons into the interior. In nanoparticles (defined in this context as having a diameter smaller than the width of the depletion layer)[56] there is no band-bending any more.

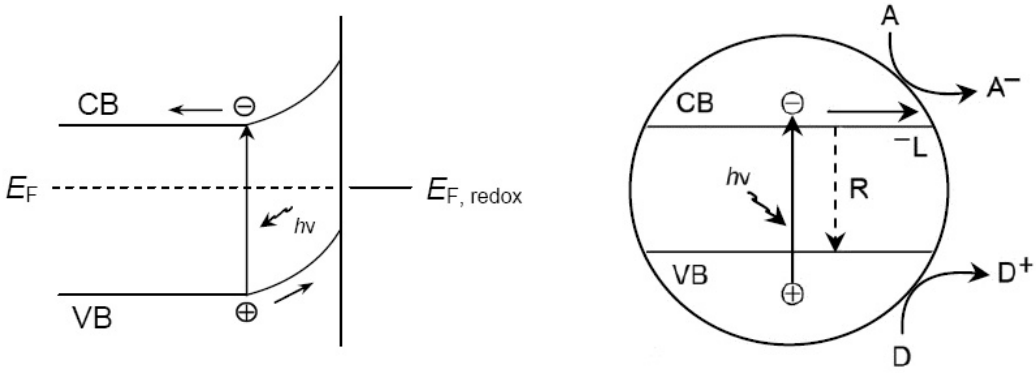

Figure 4. The consequences of creation of an electron–hole pair in a semiconductor by a light quantum *h*v. On the left, a bulk semiconductor showing the band bending resulting from depletion of electrons in the surface layer as a result of equilibration of the Fermi levels in the semiconductor (E_F) and redox couple(s) in the external environment ($E_{F,\,redox}$), in analogy to the formation of a Schottky barrier.[57] The space charge in the depletion layer creates an electric field that (in this case) drives the electrons into the interior and the positive holes to the surface; the latter there carry out oxidation of a donor D (not shown). On the right, a semiconductor nanoparticle of radius smaller than the width of the depletion layer. Electron–hole pair creation is followed by rapid migration of the charge carriers to the particle surface, where the electron carries out reduction of acceptor A and the hole oxidation of donor D.

Positive holes at the surface of the material are powerful oxidizing agents. In a terrestrial atmosphere, there is usually plenty of adsorbed oxygen and adsorbed water. The adsorbed water will partly dissociate:

$$H_2O \rightleftharpoons H^+ + OH^- \quad (1)$$

(in essence this reaction is catalysed by the titania surface, which is usually hydroxylated).[58–60] These hydroxyl ions can give up an electron to the positive holes h^+, generating highly oxidizing ·OH radicals:

$$h^+ + OH^- \rightarrow {}^{\bullet}OH \quad (2)$$

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[56] J.J. Ramsden and J. Freeman, The nanoscale. *Nanotechnology Perceptions* **5** (2009) 3–25.
[57] H. Gerischer, Ueber den Ablauf von Redoxreaktionen an Metallen und an Halbleitern III. Halbleiterelektroden. *Z. Phys. Chem.* (NF) **27** (1961) 48–79.
[58] J.J. Ramsden and R. Tóth-Boconádi, Pulsed photoelectrochemistry of titanium dioxide. *J. Chem. Soc. Faraday Trans.* **86** (1990) 1527–1533.
[59] T.L. Thompson and J.T. Yates, Surface science studies of the photoactivation of TiO_2—new photochemical processes. *Chem. Rev.* **106** (2006) 4428–4453.
[60] D. Zhang et al., Hydroxylation of the rutile TiO_2 (110) surface enhancing its reducing power for photocatalysis. *J. Phys. Chem. C* **119** (2015) 1451–1456.

The electrons reduce adsorbed molecular oxygen to form superoxide radicals:

$$e^- + O_2 \rightarrow {}^\bullet O_2^- \quad (3)$$

which in turn can pick up the proton from reaction (1):

$${}^\bullet O_2^- + H^+ \rightarrow {}^\bullet OOH \quad (4)$$

The $^\bullet$OOH and $^\bullet$OH radicals join forces to oxidize organic matter adsorbed on the surface.[61] Hydrocarbons are, thus, mineralized to CO_2 and H_2O. This general principle is also applicable to other semiconductors, and to other applications, including "water splitting" and other photosynthetic processes.[62, 63]

Among the myriads of semiconductors, few are suitable for use as photocatalytic materials. The band gap should be large to ensure that the positive holes and electrons are sufficiently powerfully oxidizing and reducing. The energetic positions of the band edges[64] should be placed appropriately with respect to the redox potentials of the substances to be mineralized and, equally importantly, with respect to the redox potentials of reactions destroying the semiconductor itself (photocorrosion). Furthermore, the material should be available at reasonable cost, be nontoxic to humans and be capable of being fabricated in a conveniently usable form.

Titanium dioxide has been recognized as one of the few currently known suitable materials. It fulfils all the criteria enunciated in the preceding paragraph. Its photoelectrochemical activity was reported in a pioneering paper by Fujishima and Honda,[65] and the operation of similar processes in nanoparticles was demonstrated a decade later.[66] Demonstration of the antimicrobial efficacity of illuminated titanium dioxide nanoparticles was reported shortly thereafter.[67] Since then there has been considerable speculation about the mechanism of antimicrobial action. This work will be briefly reviewed and discussed in Section 7.

Nanoparticles are a convenient form for the semiconductor if the photocatalytic material is to be applied as a coating. Nevertheless, unless the particles are very strongly bonded to their substrate, there must be some risk of their release into the environment and subsequent inhalation exposure.[68] A coating intended to act photocatalytically cannot incorporate a binder

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[61] S. Horikoshi et al., Photocatalyzed oxidation of water-soluble polyethylene glycol at TiO_2/H_2O interfaces. *Recent Res. Devel. Polymer Sci.* **1** (1997) 149–161.

[62] A. Mills and S. Le Hunt, An overview of semiconductor photocatalysis. *J. Photochem. Photobiol. A* **108** (1997) 1–35.

[63] A. Fujishima et al., Titanium dioxide photocatalysis. *J. Photochem. Photobiol.* C **1** (2000) 1–21.

[64] M. Gleria and R. Memming, Charge transfer processes at large band gap semiconductor electrodes: reactions at SiC-electrodes. *J. Electroanal. Chem.* **65** (1975) 163–175.

[65] A. Fujishima and K. Honda, Electrochemical photolysis of water at a semiconductor electrode. *Nature* (Lond.) **238** (1972) 37–38.

[66] D. Duonghong et al., Dynamics of interfacial electron transfer processes in colloidal semiconductor systems. *J. Am. Chem. Soc.* **104** (1982) 2977–2985.

[67] T. Matsunaga et al., Photoelectrochemical sterilization of microbial cells by semiconductor powders. *FEMS Microbiol. Lett.* **29** (1985) 211–214.

[68] The effects of such exposure might be harmful, although probably not at the release levels likely to occur (E. Bermudez et al., Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. *Toxicol. Sci.* **77** (2004) 347–357; V.H. Grassian et al., Inhalation exposure study of titanium dioxide nanoparticles with a primary particle size of 2 to 5 nm. *Environ. Health Perspectives* **115** (2007) 397–402; J. Wang et al., Acute toxicity and bio distribution of different sized titanium dioxide particles in mice after oral administration. *Toxicol. Lett.* **168** (2007) 176–185).

as in the case of paint, because the catalytic particles are thereby isolated from microorganisms arriving at the surface and the binder itself is photocatalytically degraded.

The main weakness in the suitability of titanium dioxide is the fact that its optical absorption band barely overlaps the visible part of the spectrum.[69] Hence, the catalyst is typically only weakly excited under normal conditions of illumination (daylight at sea level or standard interior illumination, even if nowadays the lighting typically used in hospitals is no longer based on incandescent filaments but on fluorescent discharge tubes or light-emitting diodes and well matches daylight in terms of its spectral distribution). Considerable efforts have, therefore, been devoted to sensitizing the photocatalytic oxidizing effect to visible light. This is discussed in more detail in Section 6.

6. Efforts to extend the photocatalytic action spectrum into the visible range

Titanium dioxide exists in three polymorphs: anatase, brookite and rutile. Rutile is the stable phase; the other two are metastable. Brookite, the hardest to synthesize and the rarest polymorph, is the least well-known regarding photocatalytic performance and other attributes. The band gap of rutile is 3.0 eV (equivalent to 414 nm; i.e. almost indigo) and it is direct, whereas that of anatase is 3.2 eV (equivalent to 388 nm; i.e. the extreme edge of the violet part of the visible spectrum) and it is indirect. Anatase is, however, a much better photocatalyst than rutile, the reasons for which are still being debated.[70] There are some differences in the effective masses of the electrons and positive holes, those of anatase being the lightest and, hence, the fastest to migrate after photoexcitation. Anatase may also have a more favourable behaviour regarding the adsorption of the reagents essential for the photocatalysed reactions: molecular oxygen and water (both from the atmosphere).[71]

Irradiation is known to create colour centres, which absorb in the visible region.[66, 72] Whether light absorbed by the centres is capable of creating the oxidizing and reducing species is unknown. The action spectrum of photocatalysis has been barely investigated.

The Bohr radii of the photoexcited charge carriers in TiO_2 are too small for their confinement to affect the position of the band edge in practically available nanoparticles, although nanoscale material will likely have interband electronic states at the abundant surfaces, which will tend to push absorption deeper into the visible range. This has not, hitherto, been well investigated.

Band-gap narrowing is in principle achievable by creating a solid solution of a semiconductor with a narrower band gap than that of pure TiO_2. In effect, this has been achieved

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[69] The band gap of anatase, the photocatalytically more active form, is normally taken to be 3.2 eV (equivalent to 388 nm; i.e., the extreme edge of the violet part of the visible spectrum). Of course, the band (optical absorption) edge simply decreases steeply (exponentially) at around that point; it does not actually becomes zero at longer wavelengths.

[70] J. Zhang et al., New understanding of the difference of photocatalytic activity among anatase, rutile and brookite TiO2. *Phys. Chem. Chem. Phys.* **16** (2014) 20382–20386.

[71] A. Sclafani and J.M. Herrmann, Comparison of the photoelectronic and photocatalytic activities of various anatase and rutile forms of titania in pure liquid organic phases and in aqueous solutions. *J. Phys. Chem.* **100** (1996) 13655–13661.

[72] V.N. Kuznetsov and N. Serpone, Visible light absorption by various titanium dioxide specimens. *J. Phys. Chem. B* **110** (2006) 25203–25209.

by doping with sulfur, creating TiS_2.[73] The photocatalytic activity of the new material was subsequently investigated, with promising results.[74] Doping with nitrogen induces localized states within the bandgap, just above the valence band.[75] This does indeed lead to a red shift of the absorption band edge of anatase, but in rutile a blue shift is observed because the valence band moves to lower energies as a result of the doping.[76] Unfortunately the N-doped materials often have poor catalytic activity and, moreover, are often thermally unstable;[77] new states within the bandgap may also serve as electron–hole recombination centres, lowering the quantum yield of photocatalysis. Attempts have been made to overcome these problems by codoping with other elements, such as molybdenum[78] and vanadium.[79] The long-term stability of these materials has not been investigated. Carbon has also been investigated as a dopant for titania, with encouraging results,[80] albeit not as good as those from nitrogen-doped material;[81] even composites with carbon nanotubes have been explored.[82]

A qualitatively different approach is to create composites using TiO_2 and materials absorbing in the visible region of the spectrum. This has been attempted using silver-doped montmorillonite (a layered silicate mineral)[83] (silver doping of titania had previously been attempted, but with disappointing results[84]). In the case of the composite, apparently in the presence of light and water vapour the silver migrates to the surface of the titania, forming useful silver oxide and silver hydroxide patches.[83] Zeolites have also been used as a support for TiO_2, with the finding of enhanced photoactivity.[85]

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[73] T. Umebayashi et al., Band gap narrowing of titanium dioxide by sulfur doping. *Appl. Phys. Lett.* **81** (2002) 454–456.

[74] J.C. Yu et al., Efficient visible-light-induced photocatalytic disinfection on sulfur-doped nanocrystalline titania. *Environ. Sci. Technol.* **39** (2005) 1175–1179.

[75] M. Batzill et al., Influence of nitrogen doping on the defect formation and surface properties of TiO_2 rutile and anatase. *Phys. Rev. Lett.* **96** (2006) 026103.

[76] C. Di Valentin et al., Origin of the different photoactivity of N-doped anatase and rutile TiO_2. *Phys. Rev. B* **70** (2004) 085116.

[77] R. Asahi et al., Visible-light photocatalysis in nitrogen-doped titanium oxides. *Science* **293** (2001) 269–271.

[78] M. Zhang et al., Molybdenum and nitrogen co-doped titanium dioxide nanotubes arrays with enhanced visible light photocatalytic activity. *Sci. Adv. Mater.* **5** (2013) 535–541.

[79] M. Zhang et al., Enhancement of visible-light-induced photocurrent and photocatalytic activity of V and N codoped TiO_2 nanotube array films. *J. Electrochem. Soc.* **161** (2014) H416–H421.

[80] K. Palanivelu et al., Carbon doping of TiO_2 for visible light photo catalysis—a review. *Carbon Sci.* **8** (2007) 214–224.

[81] M.-S. Wong et al., Visible-light-induced bactericidal activity of a nitrogen-doped titanium photocatalyst against human pathogens. *Appl. Environ. Microbiol.* **72** (2006) 6111–6116.

[82] B. Reti et al., Photocatalytic measurements of TiO_2/MWCNT catalysts having different surface coverage. *Phys. Status Solidi B* **248** (2011) 2475–2479.

[83] J. Menesi et al., Photo catalysis on silver-layer silicate/titanium dioxide composite thin films at solid/vapour interface. *Catalysis Today* **144** (2009) 160–165.

[84] A. Vohra et al. (Enhanced photocatalytic inactivation of bacterial spores on surfaces in air. *J. Ind. Microbiol. Biotechnol.* **32** (2005) 364–370 and *idem*, Enhanced photocatalytic disinfection of indoor air. *Appl. Catal. B* **65** (2006) 57–65) reported that silver doping significantly enhanced the microbicidal efficacity of undoped titania, but their results are of limited scientific value because the method of doping was not described.

[85] Y. Xu and C.H. Langford, Enhanced photoactivity of titanium(IV) oxide supported on ZSM5 and zeolite A at low coverage. *J. Phys. Chem.* **99** (1995) 1501–11507.

Composite materials have also been used to chemically enhance bactericidal activity. For example, metallic copper can be deposited on a titania film.[86] Once the cell wall is permeabilized by the photocatalytic activity (Section 7), copper ions then migrate into the interior of the bacterium, wreaking havoc. It is likely that silver acts in a similar fashion. Of course, in such cases the active lifetime of the coating will be limited, because the copper or silver will be gradually used up.

In summary, there has been a great deal of work on, especially, doping (to which extensive further references are made in the cited papers), with largely disappointing results. Even when enhanced photocatalytic activity could be demonstrated, long-term stability of the material is questionable.

It is worth noting that a different material, $NiO/SrBi_2O_4$, has been reported as being bactericidally active under visible light irradiation.[87] In comparison with the enormous amount of work that has been done on titanium dioxide, however, very little has been done with this new material. The same can be said for the much less exotic ZnO, which has a band gap and band-edge positions similar to those of TiO_2.[64] It appears to be generally felt that the large body of knowledge about TiO_2 renders work done to improve it further likely to be more fruitful than starting with a hitherto uninvestigated semiconductor showing theoretical promise.

7. The mechanism of photocatalytic destruction of microbes

This section mainly deals with the destruction of bacteria, for the work published on this topic has mainly considered them and not other kinds of microorganism.

The original work demonstrating microbial sterilization by illuminated titania used *Saccharomyces cerevisiae* (yeast, a fungus), *Escherichia coli* (a Gram-negative bacterium),[88] *Lactobacillus acidophilus* (a Gram-positive bacterium) and *Chlorella vulgaris* (a green alga).[67] The titania was in the form of powder, mixed in suspension with the suspended microorganisms. The lethal effect was enhanced if platinum (an electron transfer catalyst) was incorporated into the system. Coenzyme A (CoA) had been previously identified as the intracellular mediator of electron transfer, and it was proposed that cell death occurred by the inhibition of cell respiration. Subsequent work tended to evince the role of cell wall damage in bringing about cell death. Thus, Maness et al. proposed that lipid peroxidation, as assessed by the production of malondialdehyde from the cell membrane, disrupting functions (especially

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[86] K. Sunada et al., Bactericidal activity of copper-deposited TiO_2 thin film under weak UV light illumination. *Environ. Sci. Technol.* **37** (2003) 4785–4789.

[87] C. Hu et al., Efficient destruction of pathogenic bacteria with $NiO/SrBi_2O_4$ under visible light irradiation. *Environ. Sci. Technol.* **40** (2006) 5508–5513.

[88] It will be recalled that the bacteria can be structurally divided into two categories, Gram-positive and Gram-negative according to whether they take up a particular stain. Gram-positive bacteria (e.g., *S. aureus*) have the simpler structure: the plasma membrane made from lipids is completely surrounded by a thick (15–80 nm) peptidoglycan (murein) layer complexed with teichoic acids. Gram-negative bacteria (e.g., *E. coli*) have a thinner (10 nm) layer of peptidoglycan surrounded by an outer membrane primarily composed of lipopolysaccharide (LPS, also known as endotoxin). These structures comprise the cell wall. Beyond that, further specialized structures may be present, such as the glycocalyx (a viscous polysaccharide or polypeptide slime) and the S-layer (constituted from proteins and glycoproteins).

respiration) relying on an intact membrane, was responsible for the death of *E. coli* in the presence of illuminated titania powder.[89] Using a similar experimental setup, it was demonstrated that membrane permeability increased.[90] Subsequent work also demonstrated the gradual destruction of the cell wall in a Gram-negative bacterium.[91] A more detailed study of the kinetics of photokilling confirmed the initial step as partial decomposition of the outer membrane followed by fatal disordering of the cytoplasmic membrane, and it was also inferred that the peptidoglycan layer did not have a barrier function;[92] unlike the previous studies in which the bacteria were mixed with titania powder, in this work the bacteria were suspended in liquid in contact with a thin film of titania. Asahara et al. confirmed the efficacity of titania against a Gram-positive bacterium (*S. aureus*) and showed the existence of the photocatalytic effect, enhancing the bactericidal activity of UV radiation alone and that of an inorganic oxidizing reagent (sodium percarbonate).[93] A more elaborate composite of titania (doped with N and/or decorated with Pd) with gypsum (hydrated calcium sulfate) in the form of thin films was photocatalytically active (using 405 nm light) against methicillin-resistant *S. aureus* (MRSA).[94] Curiously, this study also showed that gypsum alone had some bactericidal effect. The researchers also showed that the titania preparations had low cytotoxicity. Silver-doped titania particles were found to be effective against *E. coli*, *S. aureus* and *P. aeruginosa* even using visible, rather than ultraviolet, light.[95] Viruses have also been investigated: illuminated titania-coated glass inactivated the influenza pathogenic agent.[96] A study similar to the previous ones using *E. coli* and *S. aureus* was reported by Sadowski et al., with the difference that the dip-coated titanium dioxide was carefully characterized photoelectrochemically prior to monitoring the bactericidal effects.[97] This study demonstrated enhancement of lethality by impregnating the titania with catechol, with the intention of enhancing the adhesion of the bacteria to the photocatalytic coating. Note that in all of these studies the microorganisms were suspended in an aqueous medium (except for the studies of Vohra et al.,[84] in which photocatalytic effectiveness in air was investigated).

In summary, the primary mechanism of lethality is oxidative cell wall destruction by $^{\bullet}$OH and $^{\bullet}$OOH. The stoicheiometry of this destruction remains uncertain. In organic chemistry,

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89 P.-C. Maness et al., Bactericidal activity of photocatalytic TiO_2 reaction: toward an understanding of its killing mechanism. *Appl. Environ. Microbiol.* **65** (1999) 494–498.

90 Z. Huang et al., Bactericidal mode of titanium dioxide photocatalysis. *J. Photochem. Photobiol. A* **130** (2000) 163–170.

91 Z.-X. Hu et al., Cell damage induced by photocatalysis of TiO_2 thin films. *Langmuir* **19** (2003) 8765–8768.

92 K. Sunada et al., Studies on photokilling of bacteria on TiO_2 thin film. *J. Photochem. Photobiol. A* **156** (2003) 227–233.

93 T. Asahara et al., The bactericidal efficacity of photocatalytic TiO_2 particle mixture with oxidiser against *Staphylococcus aureus*. *Jpn J. Infect. Dis.* **62** (2009) 378–380.

94 M. Mohl et al., Titania nanofibres in gypsum composites: an antibacterial and cytotoxicology study. *J. Mater. Chem. B* **2** (2014) 1307–1316.

95 K. Gupta et al., Photocatalytic antibacterial performance of TiO_2 and Ag-doped TiO_2 against *S. aureus, P. aeruginosa* and *E. coli*. *Beilstein J. Nanotechnol.* **4** (2013) 345–351.

96 R. Nakano et al., Photocatalytic inactivation of influenza virus by titanium dioxide thin film. *Photochem. Photobiol. Sci.* **11** (2012) 1293–1298.

97 R. Sadowski et al., Visible light induced photocatalytic inactivation of bacteria by modified titanium dioxide films on organic polymers. *Photochem. Photobiol. Sci.* **14** (2015) 514–519.

many reactions initiated by radicals turn out to be cascades (e.g., the autooxidation of lipid membranes).[98] This mechanism is in line with the well-established general mechanisms of destruction of organic molecules adsorbed on the surface of titanium dioxide, which has been investigated both experimentally and theoretically.[61] Gram-positive bacteria are generally more swiftly destroyed than Gram-negative bacteria (Kh. Hussein, personal communication).

Such results as have been reported pertain to the destruction of model surfaces inoculated with pure bacterial cultures in the laboratory. In reality, different strains of bacteria will arrive on a surface, and biofilm-forming communities are likely enough to arise.[99, 100] Although the efficacity of photocatalytic coatings in general, and titanium dioxide in particular, in destroying biofilms has not been reported, there is no principal reason why destruction should not take place.

An important question bearing on the sustainability of the deployment of photocatalytic antimicrobial coatings is whether microbes can develop resistance against them. At present there is no known route to resistance against the most probable destructive reactions.[101] Conversely, the attribute of antibiotic resistance is not expected to be relevant to the lethality of PAC. Therefore, although it has not actually been measured, we predict that, for example, all kinds of *S. aureus* (including MRSA) should be killed at the same rate.

8. Deployment of photocatalytic antimicrobial coatings in practice

One of the most important questions is whether the titanium dioxide coating is capable of destroying microbes at least as fast as they arrive at the surface. Unless this condition is maintained, the coated surfaces will in turn become coated by bacteria that will, ultimately, block light, oxygen and water from reaching the catalyst and, hence, render it impotent.

According to equations (1) to (4), the necessary ingredients for photocatalysis are light, oxygen and water.

Light. Let the incident irradiance be I. Recently this has been well studied because of interest in powering photovoltaic devices indoors.[102, 103] Although it would be easy to make an appropriate measurement, for now we shall use literature data (we note that there is a broad spread of values), suggesting that the total interior irradiance is of the order of 1 W/m^2. Of this, only about 10% is below 400 nm[104] and, hence, absorbable. If we take the average photon

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98 L.R.C. Barclay and K.U. Ingold, Autoxidation of biological molecules. 2. The autoxidation of a model membrane. A comparison of the autoxidation of egg lecithin phosphatidylcholine in water and in chlorobenzene. *J. Am. Chem. Soc.* **103** (1981) 6478–6485.

99 T.-F.C. Mah and G.A. O'Toole, Mechanisms of biofilm resistance to antimicrobial agents. *Trends Microbiol.* **9** (2001) 34–39.

100 K. Vickery et al., Presence of biofilm containing viable multiresistant organisms despite terminal cleaning of clinical surfaces in an intensive-care unit. *J. Hospital Infection* **80** (2012) 52–55.

101 J. Davies and D. Davies, Origins and evolution of antibiotic resistance. *Microbiol. Mol. Biol. Rev.* **74** (2010) 417–433.

102 O. Nizhnik et al., The availability and statistical properties of ambient light for energy-harvesting for wearable sensor nodes. *Proc. 6th Intl Conf. on Sensor Technologies and Applications* (SENSORCOMM 2012), pp. 119–122.

103 M. Müller et al., Characterization of indoor photovoltaic devices and light. *Proc. Photovoltaic Specialists Conference* (PVSC), pp. 738–743. Philadelphia: IEEE (2009).

104 D. Bugner et al., A survey of environmental conditions relative to the storage and display of photographs in consumer homes. *J. Imaging Sci. Technol.* **50** (2006) 309–319.

energy to be 0.5 aJ, this gives an absorbable flux of 2×10^{17} photons m^{-2} s^{-1}. We assume that the PAC has a thickness d of 1 μm. Near the band edge, the absorption coefficient α is quite small, around 2.5×10^3 cm^{-1}.[105] Since most practical materials (for example, the widely available Degussa/Evonik P25) seem to be a mixture of anatase (about three quarters) and rutile (about one quarter)[106] this seems to be a reasonable estimate (in any case, surface states extend the near-edge absorption towards longer wavelengths). Hence, about one quarter of the incident light will be absorbed by the coating. Since the width of the depletion layer (the region of efficient light-generated charge carrier separation) is estimated to be only a few nanometres,[105] it is likely that most of the charge carriers initially generated simply recombine. The quantum yield θ of photocatalysis in titania nanoparticles is quite high, close to unity;[107] if we use an effective thickness d_{eff} of 20 nm, we can take $\theta = 1$. The rate of supply S of oxidizing equivalents is

$$S = 2\, I_{\lambda<400\,nm}\, \theta\, d_{eff}\, \alpha \quad (5)$$

(where the factor 2 occurs because both photoelectrons and photoholes generate oxidizing equivalents, cf. equations 2–4), hence $S \approx 2 \times 10^{15}$ equivalents m^{-2} s^{-1}.

Oxygen. According to the kinetic theory of gases, the number N of molecules colliding with a surface is, per unit area and unit time,

$$N = (v_{rms}/\sqrt{3})(mN_A/V) \quad (6)$$

where v_{rms} is the root mean square speed of the gas = $3RT/M$, where R is the universal gas constant, T the absolute temperature and M the molar mass (v_{rms} is about 230 m/s for oxygen), m is the number of moles, N_A is Avogadro's number and V is the volume occupied by the m moles. At normal temperature and pressure (NTP) $V = 25$ dm^3 for $m_{total} = 1$, and $m_{oxygen} = 0.2$. Hence $N = 6.4 \times 10^{26}$ m^{-2} s^{-1} (assuming a sticking coefficient of unity). This is very comfortably in excess of the rate of generation of oxidizing equivalents.

Water. Repeating the above calculation, estimating the relative humidity to be about 50%, implying the mole fraction of water to be 0.014, and computing $v_{rms} = 415$ m/s yields $N = 8 \times 10^{25}$ m^{-2} s^{-1}, also very comfortably in excess of the rate of generation of oxidizing equivalents (water is used to replenish the surface hydroxyl ions, cf. reactions 1 and 2).

Thus, we conclude that the limiting quantity is the light.

Comparison with the microbial burden. Shiomari et al. give some hopefully representative numbers of bacteria in the air—around 100 CFU/m^3.[18] The coefficient of diffusion D of a bacterium of radius 1 μm in air can be estimated from the Stokes–Einstein equation as around 10^{-7} cm^2/s. Given that of oxygen is about 0.2 cm^2/s, we can use Graham's law

$$v_{rms,1}/v_{rms,2} = (D_1/D_2)^{1/2} \quad (7)$$

to estimate the root mean square speed of an airborne bacterium as about 0.16 m/s (Greene et al. consider airborne bacteria to be generally attached to larger water droplets and dust particles,[108]

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[105] H. Tang et al., Electrical and optical properties of TiO_2 anatase thin films. *J. Appl. Phys.* **75** (1994) 2042–2047.

[106] J. Kehres et al., Combined *in situ* small- and wide-angle X-ray scattering studies of TiO_2 nanoparticle annealing to 1023 K. *J. Appl. Crystallogr.* **43** (2010) 1400–1408.

[107] Y. Du and J. Rabani, The measure of TiO_2 photocatalytic efficiency and the comparison of different photocatalytic titania. *J. Phys. Chem. B* **107** (2003) 11970–11978.

[108] V.W. Greene et al., Microbiological contamination of hospital air. I. Quantitative studies. *Appl. Microbiol.* **10** (1962) 561–566.

so this speed may be an exaggeration). Hence, from equation (6) we can estimate the rate of arrival of bacterium at surfaces as about 10 CFU m^{-2} s^{-1}. Even if one CFU (colony-forming unit) contains 100 cells, and diffusion is augmented by convection, we are still many orders of magnitude below the rate of generation of oxidizing equivalents.

A corollary of this low rate of arrival is that the bacteria on passive surfaces are likely to remain isolated. In the absence of nutrient and congeners, biofilm formation is improbable; these bacteria will likely die anyway, even in the absence of PAC.

Taking one bacterium to occupy an area of 3 μm^2, within that area we still have the generation of 6×10^3 s^{-1} oxidizing equivalents. Of course, the presence of the bacterium will block access of oxygen and water, but in fact the surface of titanium dioxide will already be saturated with them. Hence, provided the bacteria do not actually block the light (Bateman et al.'s data suggest some attenuation)[109] photocatalytic destruction will be able to proceed. If, as suggested in Section 7, a single oxidizing equivalent is able to initiate a destructive cascade, a thin ring of activity around the periphery of the bacterium would suffice to kill it.

It is likely that once adsorbed water and oxygen are converted to radicals (reactions 2–4), they may remain for some time on the surface of the titanium dioxide, ready to react with a bacterium or other organic matter as soon as it lands on the surface. A corollary is that the PAC will remain bactericidal (presumably with gradually declining efficacity) in the dark. This is especially convenient for deployment in rooms having a diurnal rhythm of light and dark: sterilization activity remains continuous.

At present no experiments in which a defined surface concentration of bacteria is placed on a PAC-coated substratum and exposed to a defined irradiance appear to have been reported (but note the existence of an international standard for measuring the antibacterial activity of PAC[110]). Hence, the predictions of the calculations in this section cannot at present be compared with experiment.

Some limitations of the technology. Unlike many conventional (nonphotocatalytic) catalysts, titanium dioxide is not known to be inactivated (poisoned) by any material likely to be encountered in the environment. Therefore, its activity should continue indefinitely. Gross contamination (e.g., with blood splashed and dried onto a coated surface) would prevent access of light or reagents or both and render the catalyst impotent. Such soiling must, therefore, be removed by conventional means.

Titanium dioxide is attractive from the interior designer's point of view because it is colourless and transparent (provided the film scatters a negligible amount of light). It can, therefore, be applied to surfaces without altering their appearance. By the same token, it is not easy to detect, by mere visual inspection, whether a coating is still present. Given the extreme thinness of an effective coating, gross mechanical disturbance will likely remove some or all of the coating in the disturbed area. It may be that the effective management of PAC requires periodic inspection, for example using reflectometry. A simple procedure of applying a

[109] J.B. Bateman et al., Refraction and absorption of light in bacterial suspensions. *Kolloid-Z. Z. Polymere* **208** (1966) 44–58.

[110] ISO 27447:2009 *Fine Ceramics (Advanced Ceramics, Advanced Technical Ceramics)—Test Method for Antibacterial Activity of Semiconducting Photocatalytic Materials*. Geneva: International Organization for Standardization (2009).

coloured substance, such as methylene blue, known to be promptly degraded by illuminated titanium dioxide,[111] and measuring the rate of degradation spectrophotometrically under controlled illumination should suffice to assess whether a functional coating is still present. Surfaces subject to heavy abrasion, such as floors, may need to be recoated fairly frequently.

According to reactions (1) and (2), the surface of the photocatalyst should slowly become acidified. This will, of course, inhibit the dissociation of adsorbed water. Possibly, once there is an appreciable availability of adsorbed (and possibly hydrated) protons, the photoelectrons start to reduce them to molecular hydrogen:

$$2e^- + 2H^+ \rightarrow H_2 . \quad (8)$$

It is well established that this reaction is greatly facilitated by islands of catalysts like platinum.[66] The fact that the earliest paper reporting the photocatalytic killing of bacteria used platinum-loaded titania particles[67] provides a hint that the reduction of accumulated H^+ is very necessary to allow photocatalysis to proceed. This implies that reaction (3) has to compete with (8), hence the factor 2 in equation (5) is, in fact, likely to be close to unity. Nevertheless, the rate of generation of oxidizing equivalents (about 3000 oxidizing equivalents per second per bacterium) still seems to be well in excess of what is needed for microbicidal action. This is the figure that would be relevant for touch surfaces. There does not seem to be much data available regarding the amount of bacterial contamination on such surfaces. Khodavaisy et al. suggest a midrange figure of around 10^5 bacteria (CFU?) per hand,[112] equating to around 1000/cm^2. Alwis et al. have measured lavatory door knob (material not specified) contamination to be around 10 CFU/cm^2.[113] From our estimates of the supply of oxidizing equivalents, it seems that PAC could easily cope with such burdens.

9. Conclusions

Photocatalytic antimicrobial coatings, especially those based on titanium dioxide, which is the most extensively investigated material, appear to be well capable of keeping the environmental microbial burden of hospital surfaces close to zero.[114] Unlike conventional cleaning and disinfection methods, which are necessarily intermittent (and in between applications have no efficacity) and suffer from ritualistic features limiting their efficacity, the PAC, once applied, operate continuously. By maintaining the hospital interior in a state of permanent sterility, PAC, properly applied, are therefore able to replace conventional cleaning and disinfection procedures.

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[111] R.W. Matthews, Photocatalytic oxidation and adsorption of methylene blue on thin films of near-ultraviolet-illuminated TiO_2. *J. Chem. Soc., Faraday Trans.* **185** (1989) 1291–1302.

[112] S. Khodavaisy et al., Evaluation of bacterial and fungal contamination in the healthcare workers' hands and rings in the intensive care unit. *J. Preventive Med. Hygiene* **52** (2011) 215–218.

[113] W.R.D. Alwis et al., A study on hand contamination and hand washing practices among medical students. *ISRN Public Health* (2012) 251483.

[114] A study by Leng et al. (Efficacy of titanium dioxide compounds in preventing environmental contamination by methicillin-resistant *Staphylococcus aureus* (MRSA). *Intl J. Infection Control* **9** (2013) i3 [online only]) found that a PAC was not effective in preventing environmental contamination. The commercial TiO_2 product used in the study was, however, stated to incorporate a binder, which "acts as a glue to adhere the TiO_2 to the surface". Very likely the binder prevents the formation and release of oxidizing equivalents upon illumination. For the same reason, ordinary white paint is not bactericidal upon illumination.

Whether it is cost-effective to coat all interior surfaces remains open for investigation. It is highly plausible that "touch surfaces", frequently touched by the hands of healthcare workers and patients, greatly exceed in their importance for microorganism transmission passive surfaces such as walls and ceilings.

While a substantial body of work exists to show that even regular conventional cleaning or disinfection of hospital floors has no discernible effect on the environmental microbial burden, it does not necessarily follow that applying a PAC is equally ineffective because, unlike conventional methods, the PAC operates continuously.

An important general question, applicable to all cleaning and sterilization strategies, is whether there is a link between microbial burden in the hospital environment and healthcare-associated infections. Maki et al. have shown that the link is, at best, tenuous.[115] Nevertheless, the rapid emergence of multiresistant (to antibiotics) bacteria, especially during the past decade,[5] provides a new focus to the management of hospital cleaning since it is, above all, the antibiotic-resistant organisms that need to be eliminated. This consideration should at least prompt a reassessment of the roles of cleaning and sterilization to reduce environmental microbial burden, and the link between environmental burden and nosocomial infection.

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[115] D.G. Maki et al., Relation of the inanimate hospital environment to endemic nosocomial infection. *New Engl. J. Med.* **307** (1982) 1562–1566.