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Review

Gaseous and air decontamination technologies for *Clostridium difficile* in the healthcare environment

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SUMMARY

The recent data for hospital-acquired infections suggest that infection rates for meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* are beginning to decrease. However, while there is still pressure to maintain this trend, the resistance of *C. difficile* spores to standard detergents continues to present a problem for many UK hospitals trying to prevent its spread or control outbreaks. Alternative disinfection technologies such as gaseous decontamination are currently being marketed to the healthcare sector as an alternative/supplement to manual disinfection, and have been shown to be effective in reducing environmental contamination. When used correctly, they offer a complementary technology to manual cleaning that increases the probability of an effective reduction in viability and provides a comparatively uniform distribution of disinfectant. Three gaseous decontamination technologies are examined for their suitability in reducing environmental contamination with *C. difficile:* gaseous hydrogen peroxide, chlorine dioxide and ozone. Air decontamination and UV-based technologies are also briefly described. We conclude that while there is a role to play for these new technologies in the decontamination of ward surfaces contaminated with *C. difficile,* the requirement for both a preclean before use and the limited 'in vivo' evidence means that extensive field trials are necessary to determine their cost-effectiveness in a healthcare setting.

Introduction

Clostridium difficile is the leading cause of hospital-associated diarrhoea in the UK. In 2007–2008 there were 32 628 *C. difficile* infections in patients aged >65 years, with an estimated cost to the National Health Service (NHS) of at least £75 million.[1] Those persons infected with *C. difficile* excrete large numbers of vegetative cells as well as spores in their faeces.[2] Bacterial spores are a particular problem as they are 10–15 times more resistant than vegetative non-sporulating bacteria to drying, detergents, and some chemical disinfectants, and so may continue to contaminate environmental surfaces for prolonged periods.[3–5] In areas occupied by patients with *C. difficile* infection (CDI) the prevalence of *C. difficile* spores has been found to range from 9% to 59% of the surfaces sampled.[6] *C. difficile* has been isolated from ward floors, commodes, window sills, toilets, call buttons, bedrails, bedsheets, bathroom floors, chair arms, toilet seats, radiators, telephones, doorknobs, medication carts, pulse oximeter finger probes and desktop computers.[7–11] In addition, most medical or patient equipment has internal areas (handsets, keyboards, monitors, electrical beds, ventilators, etc.) which may become contaminated and are difficult to clean.[12]

To compound the problem, a positive correlation has been found between *C. difficile* on the hands of healthcare workers and its prevalence in the environment.[9] Microbial transfer from contaminated surfaces to the hands/gloves of healthcare workers (HCWs) is therefore considered likely to result in transmission to susceptible patients. This is in addition to direct pathogen transfer from contaminated surfaces to patients.[13] Bacterial acquisition from the environment is difficult to prove, and so the link between environmental contamination and the incidence of CDI is still unclear.[11,14,15]

In a hospital, cleaning of surfaces with detergent must take place, if only to improve patient confidence and staff morale. Inadequate manual cleaning and disinfection may actually increase sporulation,

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distributing *C. difficile* spores over a wider area, and necessitating additional decontamination to minimise spread.[16,17] Thorough decontamination that reduces the potential reservoir of infection has been seen by many to be a significant factor in preventing cross-transmission of the organism and, for a number of outbreaks of *C. difficile*, decontamination has been found to be effective.[15]

Environmental decontamination with a chlorine-based disinfectant such as sodium hypochlorite has been associated with a reduction, although not universal, in CDI.[11] While the application of chlorine-based disinfectants is the cheapest and considered the simplest of methods with which to tackle environmental contamination, the routine use of high level disinfectants is problematic. Their many drawbacks include: being corrosive, being inhibited by organic matter, being less effective in cleaning surfaces in comparison with detergent and hot water, and presenting an occupational and environmental risk.[18] Manual chemical disinfection is also both time- and labour-consuming. However, studies on targeted cleaning of hand-touch sites have previously been justified in terms of the overall costs of managing hospital infections.[19] Alternative technologies and approaches such as gaseous decontamination are currently being investigated for the additional benefits they may provide.[20] A brief summary of the advantages and disadvantages of these technologies is shown in Table I.

Gaseous decontamination

Gaseous decontamination is the process whereby a gas or vapour form of a chemical disinfectant, such as hydrogen peroxide or chlorine dioxide, is generated to decontaminate a specific area or room, usually one that is completely sealed. The primary advantage of gaseous decontamination technologies is that medical equipment that would otherwise be difficult to disinfect can be fully decontaminated and the inherent variability associated with manual disinfection reduced. However, in general, a manual clean with either detergent and/or a disinfectant is still generally recommended by manufacturers, and required prior to gaseous decontamination for the process to work effectively, especially when heavy contamination is expected.[21]

Hydrogen peroxide

Hydrogen peroxide is an oxidising agent which produces highly reactive hydroxyl radicals that attack DNA, membrane lipids and other essential cell components.[22] It is generally regarded as less toxic than many other gaseous decontaminants, since it breaks down to water and oxygen. The mode of action means that it will react not only with oxidisable organic matter such as faeces, but all materials and surfaces which can ultimately reduce the efficiency of the decontamination process in killing micro-organisms. Blood, in particular, contains catalase, which breaks down hydrogen peroxide and reduces its efficacy.[21] While hydrogen peroxide is compatible with a wide selection of materials, damage has been reported on contact with nylon (common in electrical connectors and conductors), neoprenes (common in sealants), some anodised aluminium surfaces and some epoxides (glues).[23] Hydrogen peroxide is also a known skin irritant. Laboratory tests on *Bacillus subtilis* spores found significant differences in the decontamination efficacy of hydrogen peroxide gas on porous and non-porous surfaces, with a 1.2 $\log_{10}$ reduction on carpet, and 2.2 $\log_{10}$ reduction on bare pine wood, compared with >7.5 $\log_{10}$ reduction on paper wallboard, formica laminate and glass.[24] Hydrogen peroxide systems were initially developed for use in pharmaceutical clean room facilities but they are now being used to decontaminate laboratories and hospitals. Industry and healthcare sector-led studies have assessed the potential of two different hydrogen

Table I
Advantages and disadvantages of hospital decontamination technologies

Technology	Efficacy	Advantages	Disadvantages
Gaseous hydrogen peroxide	>7 $\log_{10}$ reduction of spores on paper wallboards, formica and glass.[24] <2.2 $\log_{10}$ reduction on bare wood and carpet.[24]	No toxic by-products. No residue. Compatible with a wide range of material. Distribution of disinfectant across hard-to-reach/clean surfaces.	Room must be completely sealed before decontamination. Preclean is required to remove any organic material.
Chlorine dioxide	6 $\log_{10}$ reductions reported against *Bacillus atrophaeus* spores on paper and aluminium foil.[35] 6.6 $\log_{10}$ reduction on ceiling tile, 2.5 $\log_{10}$ reduction on wood.[36]	Distribution of disinfectant across hard-to-reach/clean surfaces.	Room must be sealed before decontamination. UV light will break it down. Can cause discolouration of some materials, e.g. textiles. Can penetrate certain plastics. Highly soluble in water. Humidity >65% required. Canisters of chlorine gas must be used. Explosive at concentrations >10%.
Ozone	Successfully used to reduce coliform levels by 5 $\log_{10}$ in laundry.[45] 25 ppm for 75 min has been found to give a 3 $\log_{10}$ reduction of *C. difficile* spores.[42]	Rapidly dissociates to oxygen. Distribution of disinfectant across hard-to-reach/clean surfaces.	Room must be sealed off, since effective concentrations are greater than acceptable exposure limits. Only small volumes can be effectively decontaminated; ozone's reactivity means its penetration into a room will be limited unless large concentrations are produced. Requires humidities >45% to be effective, but at humidities >80% will rapidly attack and degrade rubber. Can be noisy and produce a bad odour when in operation. Requires regular cleaning and maintenance of the filter mechanism to maintain efficiency.
Air/filter decontamination technologies	Successfully used to decontaminate air in rooms of immunosuppressed patients.[48]	Simple, easy to use. Can be used when patient is present.	
UV disinfection	Short wavelength UV (254 nm) irradiation rapidly inactivates airborne micro-organisms, including tubercle bacilli.[51] Used in the food industry to decontaminate surfaces.[54]	Simple, easy to use. Comparatively cheap.	Only effective at point of source. Organisms can be protected by shadowing. Multiple lamps may be required. Implementation for a whole room or ward is complex. Spores are notoriously resistant to UV.

peroxide-based systems for use in the decontamination of *C. difficile* wards in hospitals, with generally positive results (NHS Clean Safe Care programme, available online).

Only one study has looked at the effect of gaseous decontamination on infection rates. Boyce *et al.* performed a prospective collaborative before–after intervention study with a hydrogen peroxide vapour (HPV) decontamination system (Bioquell Ltd, Basingstoke, UK) over two consecutive 10-month periods in a hospital affected by an epidemic strain of *C. difficile*.[25] This particular system requires the decontamination zone to be completely sealed with tape, including all heating, ventilation, and air-conditioning ducts. The study found that HPV significantly reduced CDI across the five high incidence wards in which it was used, and resulted in a 53% reduction in the hospital-wide incidence ($P = 0.047$) when analysis was limited to those months when the epidemic strain was known to be present. However, since no control wards were used in this study, it is possible that the reduction in CDI was merely due to a natural fluctuation in infection rates.

A similar study compared a silver cation and dry hydrogen peroxide mist system (Sterinis, Gloster Europe SAS, France), with 0.5% hypochlorite solution in a prospective, randomised before–after trial.[6] The Sterinis system also requires the decontamination zone to be cleaned before use, but requires the room to be merely empty of people, rather than completely sealed. Prior to gaseous decontamination the rooms were sampled for *C. difficile* spores, disinfected by detergent disinfectant (or 1% hypochlorite if the room had been occupied by a *C. difficile* patient) and cleansed with tap water. The study rooms were randomised to be treated with hypochlorite (24% positive samples), or hydrogen peroxide vapour (19% positive samples). Although the number of positive samples in the rooms varied, the difference was not found to be statistically significant. Following decontamination, 12% of the hypochlorite test group samples were positive (a 50% reduction) compared with 2% of the peroxide samples (a 91% reduction). While both reductions in positive samples were significant, the Sterinis system significantly reduced ($P < 0.005$) the number of *C. difficile*-positive samples compared with hypochlorite.[6] By contrast, in laboratory tests on coupons (small discs preloaded with a known quantity of micro-organisms), there was no difference observed between the two methods; hypochlorite gave a mean 4.32 ± 0.35 $\log_{10}$ reduction in cfu within 10 min exposure, compared with a 4.18 ± 0.8 $\log_{10}$ reduction in cfu from one 3 h cycle of the peroxide system.[6]

These findings are comparable with a similar study of the same hydrogen peroxide-based system. A single cycle of decontamination was found to significantly reduce the number of *C. difficile*-positive samples by 94% ($P < 0.001$) to approximately the same level as had initially been found in low risk areas (isolation rooms in obstetric, paediatric and elective orthopaedic wards). Furthermore, several weeks following decontamination, no increase in *C. difficile* contamination was found, indicating that the measures put in place transiently controlled environmental contamination.[10] Anderson *et al.* also found similar results, and that exposure of medical equipment internally loaded with spores of *B. atrophaeus* to hydrogen peroxide was effective in 62.3% of tests.[12]

Although hydrogen peroxide is the most suitable and effective gaseous decontamination technology for use in hospital environments, it does have several drawbacks (Table I), which may preclude its use for frequent ward decontamination. The drawbacks include: the requirement to remove the patient from the room prior to performing the procedure in rooms; the need for well-trained personnel and special equipment; relatively high costs compared with manual cleaning, and the set times for decontamination cycles resulting in longer turnaround times before vacated rooms are ready for occupancy by newly admitted patients (an average of 4.5 h for a gaseous hydrogen peroxide decontamination, compared with 67 min for a manual bleach clean).[25,26] Furthermore, residue from the gaseous hydrogen peroxide solution has been shown to have cytotoxic effects, and since hydrogen peroxide vapour is absorbed by certain plastics, a long aeration phase of up to several hours in the decontamination cycle is necessary to allow the vapour to leach from the plastics, a process known as 'off-gassing'.[27,28] This time can be reduced by the use of catalytic converters, which remove the hydrogen peroxide. The long term effect of repeated exposure of plastics to hydrogen peroxide vapour has not been documented. Vapour decontamination technologies present an additional hazard, as the generation of the vapour has been known to set off fire alarms, which must therefore be covered to prevent inadvertent activation.[29]

Chlorine dioxide

Chlorine dioxide is a potent bactericidal, sporicidal and fungicidal oxidising agent, with two and a half times the oxidising power of chlorine.[30] In modern generators the production of chlorine dioxide gas generally involves passing a 2% chlorine nitrogen gas mixture over granules of sodium chlorite. It can be used at ambient temperatures of between 15 and 40 °C and needs a relative humidity of ≥65% for effective sterilisation. The gas is an orange-green colour with an odour similar to that of chlorine. To date, no studies have been published investigating its use in a clinical environment, but it has been used for the decontamination of large buildings, such as following the US anthrax outbreak in 2001 (American Media Inc., Boca Raton, FL, USA and the US Department of Justice mail facility in Landover, MD, USA) and to control the presence of moulds in buildings that presented a public health risk following the devastation caused by Hurricane Katrina in New Orleans (LA, USA).[31,32] Large building decontamination is very different from ward decontamination: the decontamination of a hospital in Oxnard (CA, USA) that was contaminated with mould required the entire contents of the hospital to be removed, before the building was covered with a large tarpaulin and then fumigated for 24 h with chlorine dioxide, at a cost of $25 million (A. Bennett, personal communication). In laboratory studies, 6 $\log_{10}$ reductions in 60 min with a 9–11 mg/L concentration of chlorine dioxide have been reported against *B. atrophaeus* spores on both paper and aluminium foil carriers.[33] In general, the higher the concentration of chlorine dioxide used during the sterilisation process the more effective the decontamination.[30]

Rastogi *et al.* compared the sporicidal efficacies of chlorine dioxide gas and vaporous hydrogen peroxide (VHP) on six building structural materials: carpet, ceiling tile, unpainted cinder block, painted steel I-beam, painted wallboard, and unpainted pine wood.[34] Log_{10} reduction values of *B. atrophaeus* spores for chlorine dioxide ranged between 2.5 (wood) and 6.6 (ceiling tile) at the 10^6 spore challenge level.[34] However, no statistically significant difference was found in the chlorine dioxide efficacy of spore killing on different materials at the three spore-loading levels at a 95% confidence level ($P = 0.05$). With VHP, a similar range of log reduction values was found from 0.8 (cinder block) to 6.1 (ceiling tile). A significant decrease in $\log^{10}$ reduction was also found when the challenge was increased to 10^8 spores.[34]

Whereas chlorine dioxide has a greater sporicidal effect than VHP, and can be used to sterilise a wide variety of enclosures, it has many limitations that inhibit its use as a decontamination technology in an active clinical environment (Table I). The gas is known to penetrate certain plastics, including polyvinyl medical device containers, is highly soluble in water, and can cause discolouration in porous fabrics.[30,35] A by-product of the incomplete chlorine dioxide gas production reaction is chlorine gas resulting in a need to monitor for raised levels of chlorine when performing sterilisation to prevent accidental exposure. Chlorine dioxide can also

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be explosive when present at high concentrations (>10% in air) which prevents it being compressed or stored commercially.[30,36]

Ozone

Ozone is a powerful oxidising agent frequently used in the pharmaceutical and food industries, and as a disinfectant of water. Ozone is effective against both Gram-negative and Gram-positive bacteria, whereas yeasts, moulds and bacterial spores are all more resistant to ozone than vegetative bacterial cells.[37–39] Ozone is relatively cheap to generate and rapidly dissociates to oxygen.[40] However, since ozone is toxic and a potent oxidiser that corrodes metals, it has not been widely investigated in the hospital environment. An exposure limit over 15 min has been set at 0.2 ppm at which concentration some people can still experience respiratory symptoms, but at which concentration, ozone has limited microbicidal efficacy.[41,42] Its primary use in the healthcare setting has been in the decontamination of laundry.[43] Cardoso *et al.* found that ozone used in a laundry processing system resulted in a 5 $\log_{10}$ reduction in the most probable number of total coliform and *Escherichia coli* present in hospital laundry rinsing water.[43] A few studies have investigated the potential for ozone as a gaseous decontaminant for the reduction of environmental *C. difficile,* with mixed results. Sharma *et al.* found a >4 $\log_{10}$ reduction in *C. difficile* cfu on various surfaces after standard ozone treatment of 25 ppm for 20 min at 90% relative humidity.[40] Another study found that 25 ppm for 75 min was required for a 3 $\log_{10}$ reduction in *C. difficile* spores.[44] By comparison, an estimated concentration of 12 ppm has been successfully used to eradicate MRSA from a domestic setting.[38] Relative humidity affects the effectiveness of sterilisation: increasing the relative humidity from 45% to 60–80% increases the biocidal activity but also increases reactivity in general.[45] At humidities of >80%, ozone will attack and degrade rubber and therefore compatibility with local materials should be considered (A. Bennett, personal communication).

Air and UV decontamination

There is relatively limited recently published information regarding the efficacy of air decontamination technologies for the control of nosocomial pathogens. Given that *C. difficile* has been isolated from air samples, lowering the bioburden in the air may have a consequent effect on reducing the risk of pathogen dissemination.[46–48] UV systems, such as upper air UV lamps, have traditionally been applied to reduce transmission of aerosol-transmitted organisms such as *Mycobacterium tuberculosis,* or to decontaminate surfaces in the food industry, and consequently modern UV technologies have been tested on non-sporulating micro-organisms that are less resistant to UV such as *Escherichia coli* and *Listeria monocytogenes.*[49–52] The use of UV for the disinfection of *C. difficile* from surfaces is doubtful.[53] Spores are innately resistant to UV, and the number of UV lamps of sufficient strength that would be required to decontaminate large surfaces renders their use for *C. difficile* decontamination prohibitive.[54] On the other hand, the potential for UV to decontaminate areas or air likely to be contaminated with vegetative cells is not without merit. Similarly, air filtration–disinfection systems are primarily intended for the decontamination of air in wards containing immunosuppressed patients or in operating theatres, and have been predominantly tested with fungal spores such as *Aspergillus* spp. In this context, they have been shown to remove/inactivate bioaerosols at significant rates, although they have not been applied for routine air decontamination in outbreak control.[46,55,56] The synergistic effects of technologies should also be investigated. It is already known, for example, that even a 1% concentration of hydrogen peroxide can increase the lethal action of UV 2000-fold.[57]

Conclusion

Detergents and disinfectants are widely used in the healthcare sector to control environmental contamination. However, there are situations where, either due to material incompatibilities or penetration issues such as access to micro-organisms that may be within electrical components/medical equipment, their use is inappropriate. Furthermore, hygienic cleaning is assessed by visual inspection which in itself is a subjective process and not an indicator of microbicidal efficacy. There may therefore be circumstances where it is appropriate to use alternative decontamination technologies to supplement, but not replace, standard cleaning and disinfection, such as additional gaseous disinfection of a ward following an outbreak. There is no single way to decontaminate, and the resistant spores of *C. difficile* present a particularly difficult challenge.

The introduction of any novel decontamination technology should be used as part of a coordinated and structured infection control intervention and, to be successful, it is essential that it be used in a manner advised by the local infection control team, following consultation with the technology manufacturer or supplier, hospital estates and domestic staff.[58] The NHS Cleaning Manual points out that skilled cleaning using traditional methods will be far more effective than unskilled incorrect use of any new cleaning/decontamination technology.[58] Before gaseous decontamination, traditional surface cleaning must still be performed. Subsequent automated gaseous decontamination applied by trained, dedicated users could provide a levelling process to improve the continuity and reliability of microbial control. The application of these technologies should be linked to microbial surveillance results and infection rates to build an evidence base. For example, the risks of transmission of *C. difficile* present on hard-to-reach surfaces is low, because the healthcare worker or patient is unlikely to come into contact with them. Because the costs of gaseous decontamination can be substantially greater than the costs of standard terminal cleaning by housekeeping personnel, additional studies are required to determine the cost-effectiveness of this decontamination technology and to identify when and where it should be used. Consideration must be given to the burdens that these technologies can bring. The need for a preclean, the time taken to empty and seal rooms or wards, the requirement to test for residual chemicals and delays in reopening wards should all be balanced against any additional microbial reduction that they offer. Only technologies with independent studies that show an improvement over that of tested chemical disinfectants in reducing *C. difficile* contamination should be applied to *C. difficile* wards. Of all the technologies currently available, the evidence suggests that hydrogen peroxide has the most potential to assist in reducing environmental levels of *C. difficile,* but it must be remembered that this technology was originally designed for the decontamination of clean rooms in the pharmaceutical industry, and that its application to the hospital environment carries with it many challenges which the technology may or may not be able to overcome.

Hospital decontamination is a complex process. Multiple surfaces made from several different materials present a considerable challenge in any event, and the additional challenge of resistant *C. difficile* spores considerably increases the magnitude of the problem. Gaseous hydrogen peroxide may be a useful additional tool in the attempts to reduce environmental contamination, but further studies are still needed to determine its practical use in reducing transmission in the hospital setting. Designing hospital surfaces, medical equipment, and furniture so that they are easy to clean and disinfect would provide an even more profound contribution to our efforts to prevent hospital-acquired infections, and open up many more opportunities for new decontamination technologies for use in the hospital environment.

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Conflict of interest statement

None declared. The views expressed in the publication are those of the authors and not necessarily those of the Health Protection Agency.

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