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Infection, infection control, and disinfectants in a challenging infection era

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Abstract

Health care-associated infections inflict a huge clinical and economic burden on public health worldwide. Bacterial resistance to antibiotics continues to escalate, and antimicrobial stewardship initiatives have yet to make a major impact. Additionally, the ability of bacteria to evade environmental threats by living within a self-produced protective biofilm and/or producing resistant spores further challenges effective infection control. The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has also amplified the burden significantly. Amidst a particularly challenging infection era, the demand for meticulous infection control and prevention practices is paramount, a key component of which is the use of appropriate disinfectants that can combat a wide variety of microbial pathogens, including diverse forms of viruses and bacteria, particularly highly tolerant spore-forming and biofilm-forming microorganisms. This review addresses the advantages and disadvantages of commonly used disinfectants such as alcohols, hypochlorite, and quaternary ammonium compounds, together with oxidizing agents such as chlorine dioxide and peracetic acid, which are gaining increasing acceptance in routine infection control practices today. Given the increasing requirements for rapid-acting disinfectants that are effective against the toughest of microorganisms (e.g. spores and biofilm), are environmentally friendly, and remain active under diverse environmental conditions, emerging oxidizing agents warrant further consideration, particularly chlorine dioxide, which offers most requirements for an ideal disinfectant, including retention of activity over a broad pH range. Given the critical importance of infection control and antimicrobial stewardship in public health and health care facilities today, consideration of chlorine dioxide as a safe, selective, highly effective, and environmentally friendly disinfectant is warranted.

Keywords: *infections; health care-associated infections; biofilms; infection control; disinfectants*

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Infections inflict a major clinical and economic burden on public health on a global scale. Within an alarmingly short timeframe, SARS-CoV-2 has disseminated uncontrollably with devastating speed and effect, infecting approximately 230 million people and accounting for more than 4.7 million deaths at the present time. While SARS-CoV-2 wreaks havoc across the globe, a longer-term, underlying, and escalating threat of bacterial resistance to antibiotics continues. Those most seriously affected by SARS-CoV-2 requiring intensive care become more susceptible to serious bacterial infections that antibiotics are increasingly less effective against. This combination exacerbates the threat to human health.

Health care-associated infections (HCAIs), that is, those acquired while in a health care setting (e.g. hospital, clinic, and long-term care), have a huge impact on patient morbidity and mortality, and on costs to health care. Prevalent HCAIs include catheter-related blood stream infections, surgical site infections, urinary tract infections, and respiratory tract infections (1). A particular spore-forming bacterium, *Clostridiodes (Clostridium) difficile*, has been reported to be responsible for 5.6% of all infections within the National Health Service (NHS) in England (2), and for a ~$1.5 billion cost burden to US health care annually (1). In a recent analysis of the impact of HCAIs on cost to the NHS in England, Guest et al. estimated 834,000 HCAIs during the period 2016/2017, costing the NHS £2.7 billion and accounting for 28,500 patient deaths (3). This study highlighted the need for strict adherence to infection control practices and guidelines.

While the global impact of antibiotic resistance and more recently the SARS-CoV-2 pandemic are widely acknowledged, another largely unappreciated factor that contributes significantly to the spread of infection is biofilm. This review will expand on the implications

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of biofilm – what it is, how it contributes to HCAIs and antibiotic resistance, and why biofilm should be acknowledged and targeted in infection control practices.

In an era of continuing bacterial resistance to antibiotics and a viral pandemic, the demand for meticulous infection control practices is greater than ever. In this respect, disinfectants and disinfection procedures are critical, and it is extremely important that disinfectants can combat a wide variety of pathogens that cause such devastating infections – including different forms of viruses and bacteria, particularly spore-forming and biofilm bacteria, which are the most difficult to kill.

What are biofilm bacteria?

Biofilm is an extracellular matrix produced by bacteria to protect themselves from the outside world. Although bacteria are widely acknowledged as existing as actively dividing single cells (sometimes referred to as planktonic or vegetative cells), they much prefer to exist as surface-attached communities. Once attached to a surface (which could be a viable tissue surface or a non-viable surface), bacteria secrete an extracellular polymeric substance around themselves to provide protection from external environmental threats such as extreme temperature, desiccation, immune cells, and antimicrobial agents. This is biofilm, and it is the natural and prevalent form of bacterial life. Biofilm dominates all habitats on the Earth's surface and has been reported to account for an estimated 80% of the approximate 1.2×10^{30} bacterial cell population (4). We see biofilm in everyday life: dental plaque on the surface of teeth, the scum in a blocked drain, and the slime in a vase of flowers are all examples of bacterial biofilm. Since the 1980s, the implications of biofilm in chronic diseases have been well-documented, and infections such as otitis media, catheter-associated urinary tract infections, and those associated with chronic, non-healing wounds are now recognized as biofilm infections (5, 6). In 2002, the United States National Institutes for Health reported that biofilms account for over 80% of human infections (7). Typically, biofilm is difficult to remove and protects bacteria from the effects of antimicrobial agents; the minimal bactericidal concentration (MBC) of bacteria protected by biofilm has been reported to be 100–1,000 times higher than that of planktonic (unprotected) bacteria (8). Consequently, biofilm infections invariably manifest as difficult-to-treat, persistent, and recurrent infections. More recently, viruses have been shown to exist within biofilm communities in flowing freshwater habitats (9), but in contrast to self-produced bacterial biofilm, viral biofilm forms via acquisition of matrix components from the infected host cell (10). The formation and existence of SARS-CoV-2 (COVID-19) biofilm has recently been hypothesized (10).

Biofilm in the health care environment

Aside from bacterial biofilm causing chronic infections, environmental biofilm is also a major concern in health care facilities. Given the ubiquity of biofilm, it will form and enable bacterial survival on non-viable surfaces such as toilet basins, sink units, drains, beds, and medical devices (e.g. endoscopes) over prolonged periods of time. A study conducted in German hospitals with high antibiotic consumption regularly detected antibiotic residues in toilets, sink siphons, and shower drains (11). Although flushing was shown to remove antibiotic residues, biofilm quickly reformed, and antibiotics were detected again. This study confirmed the ability of the biofilm to act as a reservoir for the accumulation of antibiotics in hospital sanitary units. Additionally, the transfer of antibiotic resistance genes between bacterial cells has been shown to occur 700 times more efficiently within biofilm than among free-living planktonic bacterial cells (12). Consequently, the presence of environmental biofilm in health care facilities is highly likely to enhance the spread of antibiotic resistance, in addition to facilitating bacterial survival and spread of infection (13).

Although biofilm grows most abundantly in wet conditions (i.e. wet surface biofilm), dry surface biofilm (DSB) is also a major concern in health care facilities. Biofilm containing antibiotic-resistant bacteria has been shown to persist for up to 12 months on equipment and furnishings in an intensive care unit, despite prior terminal cleansing involving detergent and bleach (14). In a UK study in three hospitals, DSBs were recovered from the surfaces of keyboards, patient folders, and hand sanitizing bottles, despite prior cleaning (15).

The ubiquity and implications of environmental biofilm within health care facilities and the criticality of effective biofilm control within infection control and prevention practices are clear.

Antimicrobial agents

Cleaning and disinfection are critical components in the control and prevention of HCAIs. Together with *antibiotics* and *antiseptics*, *disinfectants* are antimicrobial agents. The term 'antimicrobial agent' is broad-ranging and captures agents that can kill microorganisms (essentially bacteria, yeasts, fungi, and viruses) or prevent their growth. *Antibiotics* are primarily natural chemical substances produced by microorganisms to provide competitive advantage over other microorganisms. Antibiotics exhibit antimicrobial activity against specific microorganisms, for example, Gram-positive or Gram-negative bacteria, and are most commonly administered orally or intravenously to treat serious infections. *Antiseptics* are broad-spectrum chemical agents that are safe to use on viable tissues such as skin and mucous membranes but are generally too toxic to be used within the body. *Disinfectants* are similarly broad-spectrum chemical agents that are widely used on non-viable surfaces for infection control; they are too toxic to be used on or within the body. Some disinfectants may also function as antiseptics at lower, non-toxic concentrations, examples of which are included in Table 1. In health care facilities, disinfectants are routinely used to sanitize non-viable surfaces such as beds, mattresses, trolleys, toilets, bedpans, baths, incubators, ventilators, walls, floors, and ceilings, and to sterilize equipment such as endoscopes.

Microbial tolerance to disinfectants

It is important to bear in mind that different types of microorganisms have different tolerances to antimicrobial agents such as disinfectants. As indicated in Fig. 1, bacterial spores are among the most tolerant and prevalent of microorganisms in health care facilities. The ability of some bacteria to produce spores is of clinical significance because it allows the bacteria to survive under hostile environmental conditions, and the spores will germinate to form actively dividing vegetative/planktonic cells when conditions become more favorable (e.g. within the body). The most important and clinically significant spore-forming bacterium is *Clostridioides difficile*. *C. difficile* is found in the gut and can cause conditions ranging from diarrhea to life-threatening *C. difficile* infection (CDI). The bacteria readily grow in the gut (colon) and are excreted in spore-form, which can then disseminate rapidly throughout a health care facility unless effectively controlled.

Table 1. Commonly used disinfectants with examples

Antimicrobial agent/ disinfectant	Examples
Alcohols	Ethanol and isopropanol
Halogens	Chlorine, iodine, and fluorine
Peroxygens	Hydrogen peroxide, peracetic acid, and ozone
Quaternary ammonium compounds	Cetrimide and benzalkonium chloride

At the other end of the antimicrobial tolerance spectrum, lipid-enveloped viruses such as SARS-CoV-2 are among the most susceptible to disinfectants (Fig. 1). Since bacteria may be up to 100–1,000 times more tolerant to antimicrobial agents in biofilm form (8), biofilm must be considered as one of the most highly tolerant microbial forms that cannot be overlooked. All vegetative (planktonic) bacteria have the capability to exist in the much more tolerant biofilm form; examples of such pathogens include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and many antibiotic-resistant strains of bacteria.

Bearing in mind that spore-forming bacteria and biofilm bacteria are among the most difficult to treat, disinfectants should ideally provide both sporicidal and anti-biofilm activities.

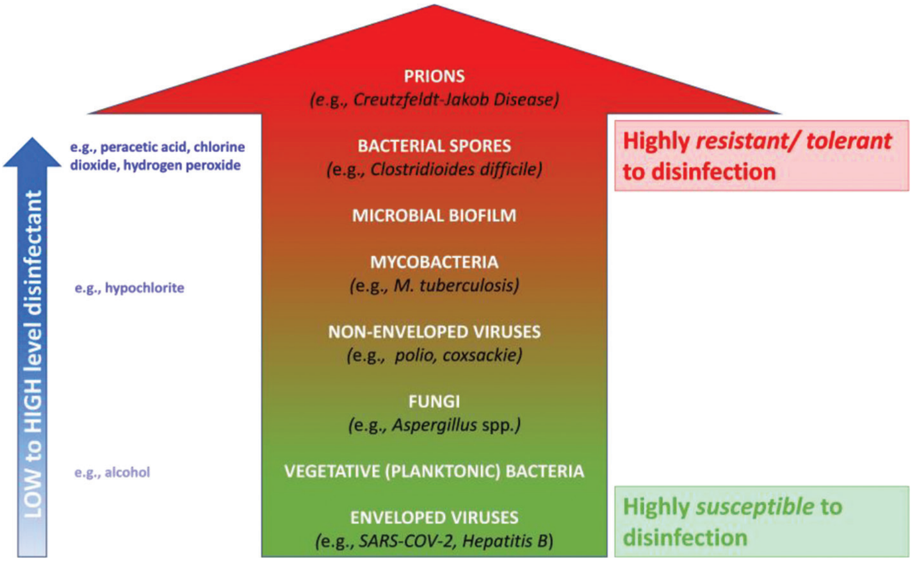

Fig. 1. Microbial tolerance to disinfectants (green = most susceptible; red = most resistant/tolerant). High level disinfectants such as chlorine dioxide, peracetic acid, and hydrogen peroxide are effective against the most resistant/tolerant bacterial forms (i.e. spores, mycobacteria, and biofilm). Note: the most resistant infectious particles (prions) require prolonged sterilization for inactivation.

Requirements for cleaning and disinfection in health care facilities

In 2019, the US Centers for Disease Control and Prevention (CDC) and Infection Control Africa Network (ICAN) published a document entitled '*Best Practices for Environmental Cleaning in Healthcare Facilities: in Resource-Limited Settings (version 2)*' (16). This document provided information on the ideal properties of disinfectants used for environmental sanitation in health care facilities, and the key requirements are summarized as follows:

1. Broad-spectrum antimicrobial activity (i.e. bacteria, spore-forming bacteria, yeasts, fungi, and viruses).
2. Rapid and sustained antimicrobial activity (fast acting and maintains residual activity on surfaces).
3. Non-irritating to skin or mucous membranes (i.e. non-toxic).
4. Maintains activity in the presence of organic matter (e.g. blood), cleaning materials (e.g. cloths), cleaning agents (detergents), and surfaces (e.g. metals and fabrics).
5. Environmentally friendly (i.e. does not produce hazardous by-products).
6. Cleansing capacity capable of removing dirt, soil, and various organic substances.
7. Remains stable in concentrated and diluted (in-use) concentrations.
8. Economical and affordable.
9. Easy to use.

Simpson et al. (17) also stated ideal criteria for a disinfectant: performance (including activity against biofilm), environment (selective reactivity and non-toxic by-products), safety, and economics (16). Based on these characteristics, chlorine dioxide was rated most highly in comparison with hypochlorous acid, hypobromous acid, and ozone (17).

In Rutala and Weber's review of disinfection practices in health care facilities, advantages and disadvantages of commonly used disinfectants were listed (Table 2) (18). Despite its widespread use in hospital antisepsis and disinfection, *alcohol* has limited antimicrobial activity (i.e. not effective against bacterial spores) and exhibits other drawbacks including reduced activity in the presence of organic matter, absence of residual activity, limited activity against non-enveloped viruses, and being flammable. Additionally, both ethanol and isopropyl alcohol have been shown to increase biofilm production in *S. aureus* and *Staphylococcus epidemidis* at concentrations ranging from 40 to 95% (19). *Sodium hypochlorite* (household bleach) is a more effective antimicrobial agent against a broader range of microorganisms (including bacterial spores), but again its activity is compromised by organic matter, it is most effective over a narrow (acidic) pH range, and it has the potential to produce environmentally hazardous by-products and can be corrosive to metals. *Quaternary ammonium compounds* such as benzalkonium chloride provide a reasonable spectrum of antimicrobial activity, they exhibit detergent properties, and they provide residual activity, but they are ineffective against bacterial spores and non-enveloped viruses, and their activity is compromised by organic matter. Like sodium hypochlorite, *peracetic acid* and *hydrogen peroxide* are oxidizing agents with superior characteristics that include a broad spectrum of antimicrobial activity (including bacterial spores), environmentally friendliness (i.e. no hazardous by-products), absence of compromise by organic matter, and surface compatibility.

Another oxidizing agent that has significant advantages over sodium hypochlorite is chlorine dioxide (ClO_2). Although ClO_2 is a chlorine compound, its chemical behavior is quite different to that of chlorine. The advantages of ClO_2 are listed as follows (17, 18) (also see Table 3):

1. **Environmental impact**. Chlorine (Cl_2) and ClO_2 are both oxidizing agents. However, whereas oxidation by ClO_2 occurs only by electron transfer (i.e. specifically with compounds that give up electrons), Cl_2 (as a halogen element) halogenates the organic compounds it oxidizes (e.g. carbohydrates, proteins, and fats) to form potentially hazardous by-products such as trihalomethanes (e.g. chloroform) and other halogenated organic compounds that are potentially carcinogenic.
2. **Selectivity.** Cl_2 is non-selective and reacts indiscriminately with organic matter. Consequently, Cl_2 is rapidly consumed in the presence of organic compounds, and disinfection is compromised until an amount greater than the chlorine demand is available. In contrast, ClO_2 is highly selective, has minimal reactivity with organic compounds, and consequently has a significantly greater capacity for disinfection and retention of antimicrobial activity over time. ClO_2 has also been shown to be a size-selective disinfectant, inflicting lethal effect on bacterial cells but not on human cells (20).
3. **pH.** The disinfection capacity of ClO_2 extends over a wide pH range of between 5 and 10, and its efficiency increases at high pH values. In contrast, sodium hypochlorite (NaOCl) is strongly influenced by pH and has no disinfection capacity above pH 8 (as hypochlorous acid [slightly acidic] transitions to hypochlorite [alkaline]) (17, 21).
4. **Antimicrobial activity.** Both NaOCl and ClO_2 exhibit broad spectrum antimicrobial activity (including bacterial spores, biofilm, and non-enveloped viruses), but

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Table 2. Advantages and disadvantages of disinfectants commonly used in health care facilities

Alcohol		Sodium hypochlorite		Quaternary ammonium compounds		Peracetic acid/hydrogen peroxide	
Advantages	Disadvantages	Advantages	Disadvantages	Advantages	Disadvantages	Advantages	Disadvantages
Bactericidal, tuberculocidal, fungicidal, and virucidal.	Does not kill bacterial spores.	Bactericidal, tuberculocidal, fungicidal, virucidal, and sporicidal (e.g. *Clostridioides difficile*).	Activity is compromised by organic matter (e.g. blood).	Bactericidal, fungicidal, and virucidal against enveloped viruses (e.g. SARS-CoV-2).	Does not kill bacterial spores.	Bactericidal, tuberculocidal, fungicidal, virucidal, and sporicidal (e.g. *Clostridioides difficile*).	Unstable.
Fast acting.	Activity is compromised by organic matter (e.g. blood).	Fast acting.	Not environmentally friendly (reacts with organic matter to produce hazardous by products such as trihalomethanes [potentially carcinogenic]).	Good cleaning capacity.	Does not kill non-enveloped viruses.	Active in the presence of organic matter.	Reacts with some metals (e.g. copper, brass).
Non-corrosive.	Slow acting against non-enveloped viruses (e.g. norovirus).	Not flammable.	Corrosive to metals.	Environmental Protection Agency (EPA) registered.	Activity affected by water hardness and cotton gauzes.	Environmentally friendly.	
No toxic residue.	No detergent or cleaning properties.	Unaffected by water hardness.	Unstable when active.	Surface compatible.	Benzalkonium chloride has been associated with asthma.	EPA registered.	
	Not EPA registered.	Reduces biofilm on surfaces.	Irritant at high concentrations.	Residual antimicrobial activity.	Activity is compromised by organic matter (e.g. blood).	Surface compatible.	
	Can damage instruments (e.g. harden rubber).	Relatively stable.					
	Evaporates rapidly making contact time compliance difficult.	EPA registered.					
	Not recommended for use on large surfaces.						
	Flammable.						

Adapted with permission from Rutala and Weber (18).

ClO_2 retains its activity in the presence of organic matter (e.g. blood spillages). Since ClO_2 is not consumed by organic matter and works over a broader pH range than other chlorine oxidizers, its disinfection capacity is maintained and significantly greater. In a study comparing the efficacy of ClO_2 and Cl_2 against a variety of bacterial isolates from clinical sources (including methicillin resistant *S. aureus, P. aeruginosa, Klebsiella pneumoniae,* and *Streptococcus pneumoniae*), ClO_2 was shown to be more effective (22). ClO_2 was also shown to be more effective than NaOCl in eliminating coliform bacteria from a variety of surfaces in a hospital out-patient department in Taiwan (23). ClO_2 has been reported to eliminate *Bacillus cereus* spores in biofilm form (24), which represents an extremely stringent situation to demonstrate potency of disinfectant activity. In the food industry and in the disinfection of cooling towers, ClO_2 has been widely used due to its excellent biofilm dispersing and bacterial disinfecting properties (17).

5. **Toxicity.** ClO_2 is size-selective and is more harmful to bacterial cells than human cells (20).

Table 3 also includes peracetic acid, another potent oxidizing disinfectant that captures many of the desirable benefits associated with chlorine dioxide, although its optimum activity is confined to a narrow pH range (25, 26).

Conclusions

Bacterial and viral infections are a huge threat to global public health, and today, this is exemplified by the devastation caused by the recent SARS-CoV-2 pandemic and the continuing escalation of bacterial resistance to antibiotics. Infection control and prevention, therefore, become paramount, and disinfectants have a major role to play in our quest to prevent the spread of infections.

This review has highlighted the inadequacies of commonly and widely used disinfectants such as alcohols, hypochlorite, and quaternary ammonium compounds when considering characteristics such as spectrum of antimicrobial activity, surface compatibility, reactivity, stability, and environmental impact. In contrast, oxidizing agents such as peracetic acid and chlorine dioxide are gaining greater acceptance because they meet optimum requirements for disinfectants to a much greater extent than some of the established disinfectants. In particular, chlorine dioxide meets many of the optimum requirements and is unique in its ability to remain effective over a broad pH range.

Given the critical importance of infection control and antimicrobial stewardship in public health and health care facilities today, consideration of chlorine dioxide as a safe, selective, highly effective, and environmentally friendly disinfectant is warranted.

Conflict of interest and funding

The author provides consultancy services to LifeClean International AB. Preparation of this manuscript was supported by LifeClean International AB, a provider of disinfectant solutions. The sponsor was not involved in the content of the manuscript.

Table 3. Comparison of chlorine, chlorine dioxide, and peracetic acid characteristics and performance

Disinfectant Characteristic	Chlorine (Cl) (e.g. sodium hypochlorite (NaOCl))	Chlorine dioxide (ClO_2)	Peracetic acid (PAA)
Oxidizing agent (electron receiving)	Yes	Yes	Yes
Halogen (salt-producing) chemical element	Yes. Oxidizes by halogenating organic matter.	No.	No
Selectivity	Non-selective. Reacts indiscriminately with organic matter, leading to rapid chlorine consumption. Disinfection is subsequently compromised until an amount of chlorine greater than the demand is available (21).	Selective. ClO_2 is highly selective and has minimal reactivity with organic matter (only attacks electron-rich bonds in the organic compounds). Consequently, ClO_2 has a significantly greater capacity for disinfection and retention of antimicrobial activity over time (17).	Selective and retains activity in the presence of organic matter (18).
Broad-spectrum antimicrobial activity	Yes. Effective against bacteria, bacterial spores, biofilm, viruses (enveloped and non-enveloped), yeasts, and fungi. Activity reduced in the presence of organic matter and at alkaline pH.	Yes. Effective against bacteria, bacterial spores, biofilm, viruses (enveloped and non-enveloped), yeasts, and fungi. ClO_2 retains its activity in the presence of organic matter (e.g. blood spillages) (21). ClO_2 effectively penetrates biofilm and kills associated bacteria (17). ClO_2 is size-selective and is more harmful to bacterial cells than human cells (20).	Yes. Effective against bacteria, bacterial spores, mycobacteria, yeasts, fungi, and viruses (18).
pH stability	No. Effective at acidic pH (as hypochlorous acid) and loses activity with increasing pH (as hypochlorite) (17, 21).	Yes. Effective over a broad pH range from acidic to alkaline [5–10] (17, 21).	Most effective at pH 6.5–7.5 (25, 26).
Environmentally friendly	No. Reacts with organic matter to form potentially hazardous by-products such as trihalomethanes (e.g. chloroform) and other halogenated organic compounds that are potentially carcinogenic (17, 21).	Yes. Minimal reactivity with organic matter and does not halogenate. ClO_2 produces harmless by-products (oxygen, sodium chloride, and water) (17, 21).	Yes. Minimal reactivity with organic matter (18). Does not halogenate and produces harmless by-products (acetic acid, oxygen, and water) (16, 27, 28).

Green: desirable; yellow: intermediate; pink: undesirable.

Ethics Approval

Not required.

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