

Antimicrobial biocides in the healthcare environment: efficacy, usage, policies, and perceived problems

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Abstract: Biocides are heavily used in the healthcare environment, mainly for the disinfection of surfaces, water, equipment, and antisepsis, but also for the sterilization of medical devices and preservation of pharmaceutical and medicinal products. The number of biocidal products for such usage continuously increases along with the number of applications, although some are prone to controversies. There are hundreds of products containing low concentrations of biocides, including various fabrics such as linen, curtains, mattresses, and mops that claim to help control infection, although evidence has not been evaluated in practice. Concurrently, the incidence of hospital-associated infections (HAIs) caused notably by bacterial pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) remains high. The intensive use of biocides is the subject of current debate. Some professionals would like to see an increase in their use throughout hospitals, whereas others call for a restriction in their usage to where the risk of pathogen transmission to patients is high. In addition, the possible linkage between biocide and antibiotic resistance in bacteria and the role of biocides in the emergence of such resistance has provided more controversies in their extensive and indiscriminate usage. When used appropriately, biocidal products have a very important role to play in the control of HAIs. This paper discusses the benefits and problems associated with the use of biocides in the healthcare environment and provides a constructive view on their overall usefulness in the hospital setting.

Keywords: biocides, efficacy, resistance, healthcare

Introduction

Chemical biocides have been used for centuries, originally for food and water preservation, although there are early accounts of their use for wound management (Lister 1867; Craig 1986; Semmelweis 1995). A clear landmark in the use of biocides in the healthcare setting was the advent of antisepsis and the use of chlorine water in the early 19th century (Rotter 1998, 2001). The 20th century witnessed a tremendous increase in the number of active compounds being used for disinfection, sterilization, and preservation, with the development of cationic biocides such as biguanides and quaternary ammonium compounds (QACs), phenolics, aldehydes, and peroxygens (Russell 1999a). The same chemical agent can be used for different applications, the main difference being the concentration at which it is employed. For example, the biguanide chlorhexidine is used for surface disinfection at 0.5%–4% volume/volume (v/v), for antisepsis at 0.02%–4% v/v and for preservation at a concentration of 0.0025%–0.01% v/v. The concentration of a biocide within a formulation or product is of prime importance for its antimicrobial activity, although there needs to be a balance between efficacy (ie, destroying microorganisms) and

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toxicity. In hospital settings, 3 levels of disinfection are recognized (high-, intermediate-, and low-level) depending upon the risk of microbial survival and transmission to patients (Rutala and Weber 1999, 2001, 2004a, 2004b). Hospital disinfection policies have a major role to play in the control of hospital-associated infections (HAIs) (Rutala 1990, 2000; Rutala and Weber 1999, 2004a; Nelson 2003; Fraise 2004). The increased usage of products containing low concentrations of commonly used biocides, such as phenolics and cationic compounds, has raised some concerns (Levy 2001; Daschner and Schuster 2004) about their overall efficacy, but also about the possible emergence of microbial resistance. Indeed, there are now multiple laboratory reports about the emergence of bacterial resistance to biocides, often as a result of exposure to a lower (sublethal) concentration (Moken et al 1997; Tattawasart et al 1999a; Thomas et al 2000, 2005; Chuanchuen et al 2001; Russell 2002a, 2004a; Walsh et al 2003). The possible development of bacterial resistance (not only to biocides, but also to antibiotics), the benefit of biocide usage, and their possible role in the emergence of multidrug-resistant bacteria, add further questions to the extensive use of biocidal products (Levy 2000; Russell 1999b, 2000, 2002a; Russell and Maillard 2000; Schweizer 2001; Bloomfield 2002). The benefits and disadvantages of biocide usage in the healthcare environment need to be carefully considered.

Biocides usage and activity

Biocides – usage and policies

Biocides are used extensively in healthcare settings for different applications: the sterilization of medical devices; the disinfection of surfaces and water; skin antisepsis; and the preservation of various formulations. In addition, there are now numerous commercialized products containing low concentrations of biocides, the use of which is controversial. Some professionals believe that the indiscriminate usage of biocides in the healthcare environment may not be justified and is detrimental in the long term, for example, by promoting the emergence of bacterial resistance to specific antimicrobials (Russell et al 1999; Levy 2000, 2001; Russell 2000, 2002b; Russell and Maillard 2000; Schweizer 2001; Bloomfield 2002; Daschner and Schuster 2004). The indiscriminate use of disinfectants in the hospital environment is not a new problem as it was raised in the 1960s (Ayliffe et al 1969), but it remains a current issue. There are diverging opinions regarding the use of biocide formulations and products for noncritical surface disinfection. While some view such use as unnecessary

(Fraise 2004), others support such a practice (Rutala and Weber 2004a). The use of biocidal products may be more appropriate only in specific situations where the risk of spreading HAIs is high (Bloomfield et al 2004; Russell 2004a). Some surfaces may only need cleaning and do not require chemical disinfection as they are rarely heavily contaminated (Table 1), whereas other medical articles need thorough cleaning with detergents and chemical disinfection, eg, wash boils, bedpans, urinal (Table 1). Thorough cleaning, washing, and drying have been shown to limit the risk of infection (Babb and Bradley 1995a). Flexible endoscopes are of particular interest, since they are now used for a wide range of diagnostic and therapeutic procedures. Gastro-intestinal endoscopes and bronchoscopes are often grossly contaminated and require special sterilization regimens involving chemical disinfectants as these medical devices are often heat sensitive. Several biocides are used for the high-level disinfection of these devices in specially designed automated machines, which clean, disinfect, and rinse the lumens and external surfaces of the flexible endoscopes. The biocides of choice are glutaraldehyde and *ortho*-phthalaldehyde, peracetic acid, alcohol, peroxygen products, chlorine dioxide, and superoxidized water for the main ones (Babb and Bradley 1995b) (Table 2). Guidelines are available from professional societies regarding the appropriate immersion time and risk assessment (BSG 1998). Overall, the incidence of post-procedural infection appears low (Fraise 2004). There are some reports describing the washer-disinfectors as a source of instrument contamination when the concentration of the high-level disinfectant is too low (van Klingeren and Pullen 1993; Griffith et al 1997), or when biofilms are present (eg, following a lack of cleaning and maintenance) (Babb 1993; Pajkos et al 2004).

The treatment of air is particularly challenging and is rarely considered necessary in hospitals, although the NHS Estates (1994) recommends good ventilation with filtered air for operating theatres, isolation rooms, and safety cabinets. In addition, prevention of airborne contaminants, particularly from the environment, is important through regular maintenance and use of biocidal treatment of static water, etc, for example to prevent the onset of *Legionella* (NHS Estates 1993; HSC 2000).

The principles of disinfection policy in healthcare facilities has been described in several reports, by Rutala (1990, 2000), Ayliffe et al (1993), and more recently by Fraise (1999, 2004). Disinfection policies should take into account the reasons and purposes for which disinfectants

Table 1 Treatment of the hospital environment and equipment

Environment/Equipment	Comments	Treatment
Walls, ceiling	Rarely heavily contaminated (surfaces need to remain dry) Occasional spillages	Occasional cleaning and drying. Chemical disinfection
Floors ^a	More heavily contaminated; only a small proportion are potential pathogens. Related to the activity on the ward (eg, number of people)	Cleaning with detergents. Disinfection recommended only in high-risk areas
Baths	Many bacteria remain on the surface after emptying the bath	Thorough cleaning with detergents. Disinfection necessary in maternity and surgical units where multiresistant bacteria might be present
Washbowls	High number of bacteria can grow if not dried properly	Thorough cleaning and drying
Toilets	Potential risk during gastrointestinal infection	Thorough cleaning with detergents, except during infection outbreaks for which chemical disinfection might be indicated
Bedpans and urinals	Potential risk during gastrointestinal infection	Thermal disinfection recommended
Crockery and cutlery	Heavily contaminated after handwash processing	Washing in a machine with minimal temperature of 50–60°C recommended
Cleaning equipment	Floor mops heavily contaminated	Heat disinfection recommended. Immersion in chemical disinfectants should be avoided
Babies' incubator	Rarely heavily contaminated but high risk of transmission	Thorough cleaning and drying of surfaces. Chemical disinfection might be considered
Respiratory ventilators	Accumulation of moisture associated with bacterial growth	Changing reservoir bag, tubing and connectors every 48 hours. Heat disinfection for respiratory circuits recommended. Use of heat-moisture exchangers or filters recommended. Use of washer–disinfectors for reusable circuits
Anesthetic equipment	Machines rarely heavily contaminated providing that the associated tubing is regularly changed	Low temperature steam or washing-machine (70–80°C) for corrugated tubing. Single use circuit preferred in some cases. Chemical disinfection to be avoided
Endoscopes	May be heavily contaminated	High-level disinfection for flexible heat sensitive endoscopes. Heat or gaseous sterilization for rigid devices
Vaginal specula and other vaginal devices	Potential risk of acquiring viral infection	Single use items are preferred. Heat sterilization recommended
Tonometers	Potentially risk of viral transmission	Chemical disinfection required ^b
Stethoscopes	Some reports of staphylococci transmission	Thorough regular cleaning with 70% alcohol recommended
Sphygmomanometer	Some reports of staphylococci transmission	Thorough washing and drying of contaminated cuff.
Linen	May be heavily contaminated	Heat (65°C) for heat-stable linen. Chemical disinfection in penultimate rinse, laundering at 40°C and dry at 60°C for heat-sensitive linen
Dressing trolleys, mattress covers, supports, curtains	May require decontamination	Thorough cleaning necessary. Decontamination by heat preferable to chemical disinfection

^a Carpets may add additional problems (Fraise 2004b)

^b In case of potential transmission of spongiform encephalopathy, disposable tonometer head should be used.

NOTE: Table compiled from information from Ayliffe 1993; Rutala 1990, 2000; Rutala and Weber 1999, 2004b; Fraise 1999, 2004; Nelson 2003.

are used, the risk of infection from equipment, or the environment and implementations of such policies (Table 2) (Fraise 2004). The benefits of the introduction of comprehensive disinfection policies on the reduction of HAIs have been described (Makris et al 2000), although their implementation has sometimes been perceived as

unsatisfactory (Cadwallader 1989; Kugel et al 2000; Sofou et al 2002). For example, infection control is an important element of safe dental practice. Chemical biocides together with detergents are used for the disinfection of surfaces (Molinari et al 1996) that can become contaminated with blood and saliva (McColl et al 1994), and for the disinfection

Table 2 Principles of disinfection policies

<i>Objectives and purposes</i>	To prevent infection but in practical terms to reduce the bioburden to a level at which infection is unlikely. Need to consider the standard of hygiene expected by patients and staff
<i>Categories of risk for patients and treatment of equipment and environment</i>	
High risk	Sterilization by heat or other methods (eg, ethylene oxide; low temperature steam formaldehyde); high-level disinfection may be acceptable (eg, GTA, OPA, PAA)
Intermediate risk	Disinfection
Low risk	Cleaning and drying usually sufficient; disinfection
Minimal risk	Cleaning and drying; disinfection in case of contaminated spillage
<i>Requirements of chemical disinfectants</i>	
Spectrum of activity	"cidal" rather than "static" activity
Efficacy	Rapid action, notably on surfaces
Incompatibility	should not be neutralized/quenched easily, eg, by hard water, soap, organic load
Toxicity	Should be minimal
Damages to products/surfaces	Corrosiveness should be minimal, especially at in use dilution. Should not damage the surface/articles to be disinfected, eg, endoscopes
Costs	should be acceptable and supplies assured
<i>Implementations of the disinfection policies</i>	
Organization	Infection control team should be responsible. Need clear cut and well defined responsibilities
Training	End users (nursing and domestic staff) should be trained appropriately. Clear schedules and supervision by trained staff should be in place.
Distribution and dilution	Staff training is essential. Suitable dispensers of disinfectants should be available
Testing of disinfectants	Need to be properly documented and assessed preferably by an independent organisation following standard protocols.
Costs	Should be considered carefully

Abbreviations: GTA, glutaraldehyde; OPA, *ortho*-phthalaldehyde; PAA, peracetic acid.

of impressions, prosthetic, and orthodontic appliances. However, a recent survey showed that a large number of dental practices have no written policies on disinfection and sterilization procedures (Bagg et al 2001). The lack of standard infection control measures has been blamed for HAIs (Nelson 2003; Rutala and Weber 2004b; Takahashi et al 2004).

Biocides – alteration of activity

The activity of a biocide depends upon a number of factors (Table 3), some inherent to the biocide, some to microorganisms. Among microorganisms most resistant to biocidal exposure are bacterial spores, followed by mycobacteria, Gram-negative, Gram-positive, and fungal microorganisms. The sensitivity of viruses usually depends upon their structure, but notably also depends on whether they possess an envelope (Maillard 2004), enveloped viruses being more sensitive to disinfection (Maillard 2001). Although there are exceptions within this summarized classification (eg, some mycobacteria are relatively sensitive to disinfection), this attempt at distinguishing microorganisms according to their susceptibility to biocides gives useful information for the selection of an appropriate biocidal agent (Russell et al 1997). However, it is not always possible to predict which microorganisms will be present

on certain surfaces, although the organic load or the extent of microbial contamination, and the presence or not of a biofilm, can be anticipated (Fraise 1999; Rutala and Weber 1999). An understanding of the factors affecting antimicrobial activity is essential to ensure that a biocidal product/formulation is used properly (Russell 2004b). As mentioned in the introduction, a biocide's concentration is probably the most important factor to affect antimicrobial activity (Table 3) (Russell and McDonnell 2000). Poor understanding of the concentration exponent can lead to microbial survival on surfaces, but also in products, and thus to infection or spoilage. Bacterial survival in biocidal formulations, notably containing QACs, has been described since the 1950s' and has been linked to inappropriate usage (Speller et al 1971; Prince and Ayliffe 1972; Ehrenkranz et al 1980; Kahan 1984), for example, a decrease in active concentration (van Klingeren et al 1993) or the incorporation of low concentrations in medical devices such as catheters (Stickler 1974; Stickler and Chawla 1988). Bacteria resistant to all known preservatives have also been reported (Chapman 1998; Chapman et al 1998). Exposure/treatment time is also essential. Standard efficacy tests often recommend a minimal contact time, such as 1 min for the testing of hygienic handwash (CEN 1997a) or 5 min for the testing of disinfectants and antiseptics (CEN 1997b).

Table 3 Factors influencing the antimicrobial activity of biocides

Factors ^a	Comments	Relevance and consequence in practice
<i>Factors inherent to the biocide</i>		
Concentration	Understand the concentration exponent (ie, the effect of dilution upon activity)	Appropriate staff training required
Contact time	Longer contact time often associated with increased activity	Appropriate staff training required
Organic load	Quench the activity of a biocide or protect microorganisms	Combination of physical (cleaning) and chemical action required
Formulation	Possible inactivation of biocide	Understand the nature of the active agent
Temperature	Important for some devices (eg, endoscope washer)	Important to understand that adequate staff training is required with certain types of equipment
pH	Affect both the biocide (stability and ionisation) and the microorganism (growth and electric charge)	Probably not as important in the healthcare environment
<i>Factors inherent to the cell</i>		
Presence of biofilm	Dormant “persister” cells difficult to eradicate. Likely to be present on equipment, certain surfaces	Combination of physical (cleaning) and chemical action required
Type of microorganisms	Will affect the choice of the agent to use. Bacterial spores: the most resistant; envelope viruses: the least resistant	Evaluation of the possible type of biocide needed
Number of microorganisms	High number more difficult to eradicate	Biocides often used in high (ie, excess) concentration. High number of cells might not be a problem

^a Factors listed in order of importance.

Decreasing exposure time is often associated with a decrease in activity, which is exemplified from kinetic inactivation studies (Tattawasart et al 1999b; Fraud et al 2001; Walsh et al 2003). Other important factors relate to the conditions in which a product is employed, mainly the presence of organic materials (which will inactivate certain biocides), or the concurrent use of a quenching agent, eg, combining a cationic agent with an anionic surfactant (Table 3) (Russell 2004b), or the use of emollient after hand washing (Walsh et al 1987; Benson et al 1990). On this latter point, information available on the effect of hand care product is sometimes contradictory. Indeed, Heeg (2001) reported that the use of hand care products did not affect the antimicrobial efficacy of hand rub formulations, although, in this case, a very limited number of products were tested. In addition, the effect of temperature on biocidal activity is important to understand in specific situations, for example, where biocidal efficacy relies upon a combination of chemical inactivation and elevated temperature (eg, certain sterilization process; automated washer-disinfector), or when a preservative-containing formulation is stored at a low temperature. Finally, pH might not be as important here as it will affect mainly the formulation (thus a concern for the manufacturer), but should not change drastically during use. It has to be noted that a change of pH can alter the biocide's ionization and hence its activity, the growth of the

microorganisms, and its overall surface charge, eg, increasing pH enhances the activity of cationic biocides (Russell 2004b). Understanding these factors is essential and the appropriate training of end users, ie, nursing and domestic staff, is important to ensure that the efficacy of a biocidal product/formulation is maintained (Widmer and Dangel 2004).

Problems associated with the use of biocides

The emergence of bacterial resistance to biocides and the possible linkage between biocide and antibiotic resistance is a major topic of discussion and concern. The emergence of bacterial resistance to biocides is not a new phenomenon and has been described since the 1950s, particularly with products containing a cationic biocide (Russell 2004a). More recently, the emergence of bacterial resistance to biocides to low (inhibitory) concentrations has been widely reported, mainly from laboratory studies, but also from environmental investigations.

Emergence of bacterial resistance – evidence from laboratory investigations

Investigating the possible emergence of bacterial resistance to various biocides is a topical subject and reports can easily be found in the literature, notably on the understanding of

Table 4 Mechanisms conferring biocide resistance in bacteria

Mechanism	Effect	Example of structures (and microorganisms)
<i>Decrease in biocide concentration</i>		
Impermeability barrier	Decrease the amount of a biocide that penetrates in the cell	Spore coats (bacterial spores), LPS (Gram-negative bacteria), mycoylarabinogalactan layer (mycobacteria)
Multidrug efflux pumps	Decrease the amount of a biocide within the cell	QacA-D, QacG and QacH, Nor A (<i>Staphylococcus aureus</i>), MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexJK, QacE, QacΔI (<i>Pseudomonas aeruginosa</i>), QacE, SilABC (<i>Klebsiella pneumoniae</i>), AcrAB-TolC, AcrEF-TolC, EmrE (<i>Escherichia coli</i>)
Degradation	Inactivate a biocide outside or within a cell	Hydrolase and reductase (<i>E. coli</i> ; <i>S. aureus</i>), aldehyde dehydrogenase (<i>E. coli</i> , <i>P. aeruginosa</i>), catalases, superoxide dismutase and alkyl hydroxyperoxidases ^a (<i>E. coli</i>)
<i>Alteration of target(s) and metabolism</i>		
Modification of target	Render the effect of a biocide ineffective ^b	Enoyl-acyl carrier reductase (<i>S. aureus</i> ; <i>E. coli</i> ; <i>Mycobacterium smegmatis</i>).
Multiplication of targets	Decreases the effective concentration of a biocide	Interaction with bacterial glycocalyx (in biofilm)
Alteration of metabolism	Decrease the detrimental effect of a biocide	Phenotypic alteration and “persisters” (bacterial biofilm)

^a Reduction of free radicals within the cell (eg, following exposure to an oxidising agent);

^b Has only been observed with the bisphenol triclosan.

the basis of such resistance. Low to intermediate levels of resistance have been observed in most cases, although from time to time high-level resistance has been reported, eg, with the bisphenol triclosan (Sasatsu et al 1993; Heath et al 1998, 2000), or with the chemosterilant glutaraldehyde (Griffiths et al 1997; Manzoor et al 1999; Fraud et al 2001; Walsh et al 2001), and oxidizing agents (Dukan and Touati 1996).

There is now a better understanding of the overall mechanisms that enable bacteria to withstand exposure to low concentrations of a biocide (Table 4) (Poole 2002; Cloete 2003). As mentioned earlier, some microorganisms are better at surviving a biocidal treatment than others, primarily through their intrinsic properties and impermeability. The impermeability barrier, encountered in spores (Russell 1990; Russell et al 1997; Cloete 2003), but also in vegetative bacteria such as mycobacteria, and to some extent, Gram-negative bacteria, limits the amount of a biocide that penetrates within the cell (Denyer and Maillard 2002; Lambert 2002). The role of specific cell structure, such as lipopolysaccharides (LPS) in Gram-negative bacteria (Denyer and Maillard 2002) and the mycoylarabinogalactan layer in mycobacteria (Lambert 2002), in this resistance mechanism has been demonstrated by the use of permeabilizing agents such as ethylenediamine tetraacetic acid (EDTA) (Ayres et al 1998; McDonnell and Russell 1999; Denyer and Maillard 2002), or organic acids (Ayres et al 1993; 1998), and cell wall inhibitors such as ethambutol (Broadley et al 1995; Walsh et al 2001). The insusceptibility of Gram-negative bacteria to biocidal agents can be decreased further by a change in overall hydrophobicity

(Tattawasart et al 1999a), outer membrane ultrastructure (Tattawasart et al 2000a, 2000b), protein content (Gandhi et al 1993; Brözel and Cloete 1994; Winder et al 2000), and fatty acid composition (Jones et al 1989; Méchin et al 1999; Guérin-Méchin et al 1999, 2000).

Bacteria are also able to decrease the intracellular concentration of toxic compounds by using a range of efflux pumps (Nikaido 1996; Paulsen et al 1996a; Levy 2002; McKeegan et al 2003), which can be divided into five main classes: the small multidrug resistance (SMR) family (now part of the drug/metabolite transporter [DMT] superfamily), the major facilitator superfamily (MFS), the ATP-binding cassette (ABC) family, the resistance-nodulation-division (RND) family and the multidrug and toxic compound extrusion (MATE) family (Brown et al 1999; Borges-Walmsley and Walmsley 2001; Poole 2001, 2002, 2004; McKeegan et al 2003). The involvement of multidrug efflux pumps in bacterial resistance to various compounds including QACs, phenolics, and intercalating agents has been widely reported (Tennent et al 1989; Littlejohn et al 1992; Lomovskaya and Lewis 1992; Leelaporn et al 1994; Heir et al 1995, 1999; Sundheim et al 1998), particularly in *Staphylococcus aureus* with identified pumps such as QacA-D (Rouche et al 1990; Littlejohn et al 1992), Smr (Lyon and Skurray 1987), QacG (Heir et al 1999), and QacH (Heir et al 1998) and in Gram-negative such as *Pseudomonas aeruginosa*, with MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexJK (Schweizer 1998; Chuanchuen et al 2002; Morita et al 2003; Poole 2004) and *Escherichia coli* with AcrAB-TolC, AcrEF-TolC, and EmrE (Moken et al 1997;

McMurry et al 1998a; Nishino and Yamagushi 2001; Poole 2004) (Table 4).

Another mechanism that can contribute to the reduction in the concentration of a toxic compound is degradation (Table 4). Degradation has been well described for metallic salts with an enzymatic reduction (Cloete 2003) and for aldehydes with the involvement of aldehydes dehydrogenase (Kummerle et al 1996). The degradation of phenols, such as triclosan, by environmental strains (Hundt et al 2000) has been reported, but there is little evidence that such degradation takes place in clinical isolates. In addition, some bacteria express enzymes such as catalases, superoxide dismutase, and alkyl hydroxyperoxidases to prevent and repair free radical-induced damage caused by oxidizing agents (Dempsey 1996).

Finally, although the modification of a target site is a well-known mechanism of bacterial resistance to antibiotics (Chopra et al 2002), it does not usually occur with biocide—with possibly one exception, the bisphenol triclosan. This phenolic compound has been shown to interact specifically with an enoyl-acyl reductase carrier protein (Heath et al 1999; Levy et al 1999; Roujeinikova et al 1999; Stewart et al 1999), the modification of which was associated with low-level bacterial resistance to this compound (McMurry et al 1999; Heath et al 2000; Parikh et al 2000). The inhibition of the fatty acid biosynthesis might be involved in the growth-inhibitory effect of triclosan, but other mechanisms were involved in its lethal activity (Gomez Escalada et al 2005).

Some of the mechanisms described above are intrinsic to the microorganisms; ie, a natural property. The acquisition of resistance is of notable concern since a previously sensitive microorganism can become insusceptible to a biocide (Russell 2002b) or a group of antimicrobials through, eg, the acquisition of multidrug resistant determinants (Lyon and Skurray 1987; Silver et al 1989; Kücken et al 2000; Bjorland et al 2001). Acquired resistance can arise through several processes, eg, mutations, the amplification of an endogenous chromosomal gene, and the acquisition of genetic determinants (Lyon and Skurray 1987; Paulsen et al 1993; Poole 2002).

Phenotypic variations resulting from biocidal exposure might lead to bacterial resistance (Chapman 2003) and this is now well supported by documented laboratory evidence. This is an issue since phenotypic alterations can lead to the emergence of resistance to several unrelated compounds in vitro (Walsh et al 2003; Thomas et al 2005). Phenotypic variation and antimicrobial resistance also concern bacterial

biofilms, which are increasingly associated with bacterial contamination and infection, eg, implants, catheters, and other medical devices (Costerton and Lashen 1984; Costerton et al 1987; Salzman and Rubin 1995; Gilbert et al 2003; Pajkos et al 2004). Bacteria in biofilms have been shown to be more resistant to antimicrobials than their planktonic counterparts (Allison et al 2000). Resistance results from a multicomponent mechanism involving phenotypic adaptation following attachment to surfaces (Brown and Gilbert 1993; Ashby et al 1994; Das et al 1998), impairment of biocide penetration, and enzymatic inactivation (Sondossi et al 1985; Giwerzman et al 1991; Huang et al 1995; Gilbert and Allison 1999), and the induction of multidrug resistance operons and efflux pumps (Maira-Litran et al 2000).

Emergence of bacterial resistance to biocides and antibiotics – evidence from laboratory investigations

While there is ample evidence from laboratory studies of bacterial adaptation to biocides, linkage to antibiotic resistance is not always clear cut (McMurry et al 1998a, 1999; Tattawasart et al 1999a; Thomas et al 2000; Winder et al 2000; Walsh et al 2003; Nomura et al 2004). Several laboratory investigations have explored a possible linkage between bacterial resistance to antibiotics and different biocides such as the bisphenol triclosan (Moken et al 1997; McMurry et al 1998a; Chuanchuen et al 2001; Cottell et al 2003), the biguanide chlorhexidine (Russell et al 1998; Tattawasart et al 1999a), and QACs (Akimitsu et al 1999; Walsh et al 2003). Similar mechanisms of resistance have been identified such as impermeability (Tattawasart et al 1999a), the induction of multidrug efflux pumps (Levy 1992; Moken et al 1997; Schweizer 1998; Zgurskaya and Nikaido 2000; Noguchi et al 2002), over expression of multigene components or operons (Levy 1992) such as *mar* (Moken et al 1997; McMurry et al 1998a), *soxRS* and *oxyR* (Dukan and Touati 1996; McMurry et al 1998a; Wang et al 2001), and the alteration of a target site (McMurry et al 1999).

Emergence of bacterial resistance – evidence from investigations in situ

It has been suggested that the use of biocide in healthcare environments leads to the emergence of antibiotic resistance in bacteria, although the evidence in situ is lacking overall (Russell 2002a) or does not support such a claim (Lambert 2004). Nevertheless, there have been a number of cases

linking biocide usage and emerging antibiotic resistance. For example, the use of silver sulphadiazine for the treatment of burn infection was associated with sulphonamide resistance (Lowbury et al 1976; Bridges and Lowbury 1977). Likewise, the use of chlorhexidine scrub-based preoperative showers might be associated with the emergence of methicillin-resistant *S. aureus* (MRSA) (Newsom et al 1990). The use of the biguanide in catheters for long-term indwelling catheterization was linked to the emergence of Gram-negative bacteria with multiple antibiotic resistance (Stickler 1974; Stickler and Chawla 1988). The bisphenol triclosan has also been associated with such cross-resistance (Chuanchuen et al 2001; Levy 2001; Aiello et al 2004; Schmid and Kaplan 2004) although evidence in situ is scarce and recent field investigations failed to make such a link (Lear et al 2002; Sreenivasan and Gaffar 2002; Cole et al 2003; Lambert 2004). The heavy use of QACs has also been blamed for the dissemination of *qac* genes and the spread of efflux pumps (Paulsen et al 1996a, 1996b; Heir et al 1998, 1999; Mitchell et al 1998; Sundheim et al 1998), although further evidence is needed to confirm such a link (Russell 2002a).

Other considerations

Biocides are chemical agents that are usually toxic at relatively high concentration, not only for the end user, but also for the environment (Dettenkofer et al 2004). The toxicity of some biocides has been particularly well described, eg, the high-level disinfectant glutaraldehyde, the use of which has been associated with dermatitis and occupational asthma (Di Stephano et al 1999; Shaffer and Belsito 2000; Vyas et al 2000). Toxicity and irritation have also been reported with other biocides such as chlorhexidine (Waclawski et al 1989), povidone iodine (Waran and Munsick 1995), and other disinfectants and antiseptics (Sweetman 2002), although such incidence is infrequent (Rutala and Weber 2004a). Hypersensitivity and irritation caused by antiseptics might account for the low compliance in handwashing among healthcare workers (Pittet 2001). A recent study found that hospital staff using disinfectants might not appreciate the health risks associated with a product (Rideout et al 2005).

The future of biocides in the healthcare environment

There is no doubt that biocides will continue to play an important role in the prevention of infection in the healthcare environment, although some caution is needed as to their

usage and the type of products that should contain antimicrobials. For disinfection and antisepsis purposes, chemical biocides are usually used at high concentrations, exceeding their bacterial minimum inhibitory concentrations many times to achieve a rapid kill. At such concentrations, a biocide will interact with multiple target sites (Maillard 2002), and the emergence of bacterial resistance is therefore unlikely.

The increased usage of biocide in formulations and products is probably driven by the impetus to control and reduce the spread of HAIs (Favero 2002), by an increase in public awareness for microbial infection and contamination, and hygiene (Aiello and Larson 2001; Bloomfield 2002; Favero 2002), and by strong and profitable commercial interests. The use of such products needs to be balanced between the clear benefit of controlling infection and the potential risk associated with usage, not only in terms of emerging microbial resistance, but also their toxicity and environmental pollution (Daschner and Dettenkofer 1997; Russell 2002b; Gilbert and McBain 2003; Bloomfield et al 2004; Dettenkofer et al 2004; Rutala and Weber 2004a). In this respect, the benefits of using biocides on noncritical surfaces to prevent the transmission of HAIs should be evaluated further (Bloomfield et al 2004). Assessing the role of biocides in controlling nosocomial infection or the value of a disinfection policy is difficult to evaluate in situ, although such information is valuable for the selection of the appropriate regimens (Fraise 2004). For example, a recent study showed that the use of alcohol hand gel reduced HAIs significantly (Zerr et al 2005). For a biocidal formulation/policy to be effective, (1) knowledge of the chemical biocide (ie, activity and limitation), (2) training of end users, and (3) compliance, are essential. It has to be noted that, when possible, physical processing, eg, heat sterilization, offers many advantages over chemical disinfection and should be the method of choice when appropriate (Fraise 2004). Some authors and institutions have advocated the rotation of biocidal formulations despite a lack of scientific evidence of the benefits of such practice (Murtough et al 2001). A clear understanding of the mechanisms of action, the factors affecting their activity, and the problems associated with specific practice is essential and may contribute to the improvement of a biocidal product, in terms of activity, but also usage. For example, improved compliance to hand hygiene in healthcare settings was observed with the introduction of hand rub and alcoholic rub products (Pittet 2001; Boyce and Pittet 2002).

Likewise, understanding of microbial survival to disinfection, limitation, and activity of “chemical sterilants” has led to the commercialization of formulations with improved efficacy for the high-level disinfection of heat-sensitive medical devices (Rutala and Weber 1999; Maillard 2002).

Finally, there have been some interesting developments in the use of biocides for the treatment and prevention of potential infections. In the dental field, light-activated biocides such as toluidine blue are being explored for the treatment of root canals (Walsh 2003; Wilson 2004). In the medical field, the incorporation of biocide combinations (eg, phenolics, metallic salts) into implants (Petratos et al 2002), and catheters (Hanazaki et al 1999), and other medical devices (Masse et al 2000; Jones et al 2003) is a fast advancing field of research, although biocide-containing medical devices may be of some concern (Masse et al 2000; Stickler 2002). Advances in polymer technology and biocidal research will undoubtedly contribute to the emergence of novel biocidal product or biocide-coated/containing medical devices with selected usage and improve efficacy.

Conclusion

The last 50 years have witnessed an important increase in the number of biocides and their usage in the healthcare environment. When used correctly (ie, compliance with disinfection/antiseptis regimens), biocides have an important role to play in controlling infection (Larson et al 2000; Russell 2002a). There is still some uncertainty as to the extent of their use in the healthcare environment. Should they be reserved for the disinfection of critical and semi-critical items/areas only, or should they be used also on noncritical devices/surfaces? Should the use of biocide-embedded products (eg, plastics, fabrics) be encouraged or banned? There is no doubt that the use of chemical biocides creates a selective pressure. However, it is yet unclear in practice whether such pressure favors the emergence of bacterial resistance. It is pertinent to note that the development of antibiotic resistance as a result of the selective pressure exerted by their intensive use, and sometimes misuse, is well documented (WHO 2000). Monitoring the susceptibility profile of hospital isolates to biocides might therefore be indicated. This would provide useful information as to whether bacterial survival in the healthcare setting following exposure to chemical biocides results from the bacterial resistance mechanisms (eg, biofilm persistence) or from disinfection failure following

inappropriate usage. More research is needed to better assess the effect and efficacy of biocidal policies in practice.

This paper focused mainly on bacterial infection and did not expend on infection/contamination caused by other microorganisms such as viruses, fungi, and prions. Among these microorganisms, prions are the most resistant to biocides and when the presence of these agents is suspected, the use of single-use items is recommended. If this is not possible, special sterilization regimens should be employed (Taylor and Bell 1993; Taylor 2001; Fichet et al 2004; Rutala and Weber 2004b). Nonenveloped viruses might also be particularly resilient to disinfection (Maillard 2001, 2004), although the virucidal efficacy of biocides and biocidal policies in situ is poorly documented. Again, more investigation is needed to gain a better understanding of the survival capabilities of these microorganisms in the healthcare environment following disinfection.

Biocides are essential in preventing and controlling infections in the healthcare environment and the benefits from their usage currently outweigh possible disadvantages (Rutala and Weber 2004a). Disinfection of noncritical surfaces and items, and the usage of biocide-containing products, need to be reviewed, although the incorporation of biocides into medical devices to prevent bacterial infection is promising, if controlled and assessed appropriately.

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