Antiseptic “Resistance”: Real or Perceived Threat?

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Biocides (antiseptics, disinfectants, preservatives, and sterilants) are critical components of intervention strategies used in clinical medicine for preventing the dissemination of nosocomial diseases. Biocides are also used in community environments for personal hygiene and to prevent cross-contamination with foodborne pathogens. In vitro studies suggest that exposure to biocides results in reduced susceptibility to antibiotics and biocides by intrinsic or acquired mechanisms of resistance. In addition, microorganisms have adapted to biocide exposure by acquiring plasmids and transposons that confer biocide resistance, the same survival strategies to disseminate acquired mechanisms of resistance to biocides as they have for resistance to antibiotics. The scientific community must weigh the risks and benefits of using biocides in clinical and community environments, to determine whether additional precautions are needed to guide biocide development and use. At present, insufficient scientific evidence exists to weigh these risks, and additional research is needed to allow appropriate characterization of risks in clinical and community environments.

One of the most important contributions to modern medicine is Semmelweis’ mandate that physicians wash their fingers with chlorine after examinations to prevent puerperal (childbed) fever, resulting in decreased morbidity and mortality in the maternity ward [1]. Semmelweis’ study is significant because it demonstrates the effect of the use of topical antiseptics as an intervention strategy for reducing the spread of clinical disease. Now, biocides (antiseptics, disinfectants, preservatives, and sterilants) are an integral component of the practice of clinical medicine, serving to prevent the dissemination of nosocomial pathogens in the hospital environment [2]. Biocides are also used in the community (i.e., in homes, day care centers, nursing homes, and food-service establishments), primarily as antiseptics, disinfectants, and preservatives, as an integral part of good hygienic practices [3, 4]. However, as with more-frequent use of antibiotics, increased use of biocides contributes to the emergence and/or selection of pathogens that are less susceptible not only to biocides but also to antibiotics [5, 6]. In this article, “biocide” is a general term used to describe chemical agents that inactivate or kill vegetative microorganisms (table 1).

The present article uses select examples to illustrate the mechanisms by which biocides exert biological effects, the mechanisms that influence the biological activity of biocides, and the possible consequences of these mechanisms on the efficacy of biocides in the clinical setting. Although the use of biocides in the community is not discussed, concepts and issues pertinent in the clinical setting are generally applicable to the community setting, because the intended outcome of biocide use is the same: prevention of the dissemination of pathogens [7–9].

SUSCEPTIBILITY TESTING OF BIOCIDES: WHAT DOES IT MEAN?

In the clinical setting, in vitro susceptibility tests are performed and interpretative standards are used to determine whether antibiotic treatment is likely to be effective for treatment of infection due to a specific pathogen. Interpretative standards for antibiotics are based on the spectrum of activity, achievable serum levels (pharmacokinetics), pharmacodynamic parameters of the antimicrobial class, and results of clinical trials performed during the investigational stages of drug development. For example, interpretative standards suggest that the use of amoxicillin to treat Enterobacteriaceae exhibiting an amoxicillin MIC of $\leq 8.0 \mu g/mL$ is likely to result in successful treatment, whereas interpretative standards for treatment of isolates exhibiting an amoxicillin MIC of $\geq 32 \mu g/mL$ suggest that therapy is likely to fail.

Internationally recognized and standardized methods of in
vitro susceptibility testing are not available for topical antiseptics or biocides, and prediction of clinical success has not been correlated with clinical outcome. Currently, biocide susceptibility testing is performed with methods developed for systemic antibiotic susceptibility testing. However, biocide resistance in microorganisms cannot be interpreted in the same manner that resistance to systemic antibiotics is interpreted. At present, interpretative criteria are not necessary for biocides and other topical antimicrobial therapies, because in-use concentrations are often orders of magnitude greater than the antimicrobial MICs investigated in the laboratory setting.

Results of biocide susceptibility tests are used to monitor changes in the susceptibility patterns of microorganisms. Such changes lead to investigations of the mechanisms of action conferring nonsusceptibility and, subsequently, cross-resistance to antibiotics. In this review, for reasons discussed elsewhere, “nonsusceptible” instead of “resistance” is used to describe microorganisms with reduced susceptibility patterns that do not conform to those of wild-type populations.

The pharmaceutical industry and regulatory agencies use in vitro and in vivo tests to assess the effectiveness of biocides in specific clinical applications [10, 11]. The US Food and Drug Administration (FDA) uses surrogate microorganisms and clinical simulation protocols to mimic real-world conditions for surgical hand scrubs, preoperative skin prep solutions, and health care personnel hand washes to assess the efficacy of topical antiseptics. However, the predictive efficacy of the FDA’s surrogate testing methods still requires validation in clinical settings [10].

**BIOCIDE MECHANISM(S) OF ACTION**

Techniques used to study antibiotic mechanisms of action are useful for evaluating biocide mechanisms of action. Such techniques are used to analyze biocide effects on membranes (via microscopic examination of cells, study of model membranes, and examination of uptake, lysis, and leakage of intracellular components) and intracellular components (such as the interactions between macromolecules and their biosynthetic processes and the inhibition of oxidative phosphorylation, enzyme activity, and electron transport) [12]. By means of these techniques, biocide targets and mechanisms of action are being characterized. A summary of select biocides used in health care settings, as well as their targets, is presented in table 2.

Although the antimicrobial spectrum of activity and the efficacy of biocides are documented, a complete characterization of the mechanisms of action is lacking. Mechanisms of action depend on the chemical nature of the biocides, the pathogens used in their evaluation (e.g., gram-positive bacteria, gram-negative bacteria, yeasts, and viruses), and the test conditions (e.g., concentration, pH, duration of exposure, and temperature). In general, the biocide initially binds to targets within the cell wall to disrupt the latter’s integrity and then penetrates the cell wall and interacts with cytoplasmic constituents [13]. Information presented in table 2 describes multiple targets of biocides and confirms the accepted premise that biocides, unlike antibiotics, have multiple targets within the microbial cell when used at recommended concentrations. This multiple-target effect confers bactericidal activity and prevents the emergence of resistant bacteria. Detailed presentations and discussions of the mechanisms of action of biocides are presented elsewhere [12, 13].

### MECHANISMS OF NONSUSCEPTIBILITY TO BIOCIDES

A review of current literature regarding the genetic and biochemical basis of nonsusceptibility to antiseptics reveals 2 mechanisms of nonsusceptibility: intrinsic and acquired [3, 12, 14, 15].

**Intrinsic nonsusceptibility.** The intrinsic mechanism of nonsusceptibility to antiseptics is an innate characteristic of the bacterial genome and is mediated by impermeability, efflux (particularly in gram-negative bacteria), biofilms, and enzymatic degradation. Structures that confer impermeability include the waxy cell walls of mycobacteria, the cell walls of gram-negative bacteria, and the spores of spore-forming microorganisms [3]. Among vegetative bacteria, biocide susceptibility is a function of the permeability of the biocide through the cell wall; gram-positive bacteria are more permeable and susceptible to biocides, whereas mycobacteria and gram-negative bacteria, which have a more complex cell wall, are less permeable and susceptible.

The highly hydrophobic cell wall of mycobacteria is composed
<table>
<thead>
<tr>
<th>Biocide</th>
<th>Sample agents</th>
<th>Uses</th>
<th>Target and mechanism(s) of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols</td>
<td>Ethanol, isopropanol, n-propanol</td>
<td>Antisepsis, disinfection, preservation</td>
<td>Penetrating agents that cause loss of cellular membrane function, leading to release of intracellular components, denaturing of proteins, and inhibition of DNA, RNA, protein, and peptidoglycan synthesis.</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>Glutaraldehyde, formaldehyde&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Disinfection, preservation, sterilization</td>
<td>Cross-linking agents that interact with unprotonated amines in outer cell wall, resulting in loss of cell wall function. Cross-linking of thiol, sulphhydryl, and amino groups results in inhibition of protein, DNA, and RNA synthesis.</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Chlorhexidine alexidine</td>
<td>Antisepsis, antiplaque, disinfection, preservation</td>
<td>Membrane-active agents that damage cell wall and outer membrane, resulting in collapse of membrane potential and intracellular leakage. Enhanced passive diffusion mediates further uptake, causing coagulation of cytosol.</td>
</tr>
<tr>
<td>Bisphenols</td>
<td>Triclosan</td>
<td>Antisepsis, deodorant, disinfection, preservation</td>
<td>Agents that bind to enoyl-acyl carrier protein reductase, causing inhibition of fatty acid biosynthesis.</td>
</tr>
<tr>
<td>Halogen-releasing agents</td>
<td>Iodine, chlorine</td>
<td>Antisepsis, disinfection, cleaning</td>
<td>Highly active oxidizing agents that destroy cellular activity of proteins. Disrupts oxidative phosphorylation and membrane-associated activities. Iodine reacts with cysteine and methionine thiol groups, nucleotides, and fatty acids, resulting in cell death.</td>
</tr>
<tr>
<td>Halophenols</td>
<td>Chloroxylenol</td>
<td>Antisepsis, preservation</td>
<td>Little studied and relatively unknown.</td>
</tr>
<tr>
<td>Peroxogens</td>
<td>Hydrogen peroxide&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Disinfection, preservation</td>
<td>Hydrogen peroxide is an agent that produces hydroxyl free radicals that function as oxidants, which react with lipids, proteins, and DNA. Sulphhydryl groups and double bonds are targeted in particular, thus increasing cell permeability.</td>
</tr>
<tr>
<td>Phenols</td>
<td>Phenol</td>
<td>Disinfection, preservation</td>
<td>Agents that increase cytoplasmic membrane permeability, resulting in progressive leakage of intracellular constituents. Permeability to protons results in dissipation of proton motive force and uncoupling of oxidative phosphorylation, coagulation of cytoplasm, and eventual cell lysis.</td>
</tr>
<tr>
<td>Quaternary ammonium compounds</td>
<td>Benzalkonium chloride, cetrimide</td>
<td>Antisepsis, disinfection, preservation, cleaning</td>
<td>Membrane-active agents that damage cell wall and cytoplasmic membrane, mediated by binding to phospholipids, resulting in loss of structural integrity of the cytoplasmic membrane; enhances further uptake and induces leakage of intracellular components and cell lysis.</td>
</tr>
<tr>
<td>Vapor-phase agents</td>
<td>Ethylene oxide, formaldehyde&lt;sup&gt;a&lt;/sup&gt;, hydrogen peroxide&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Disinfection, sterilization</td>
<td>Ethylene oxide and formaldehyde: alkylating agents that react with amino, carboxyl, sulphhydryl, and hydroxyl protein and nucleic acid groups to affect purine nucleoside and nucleic acid synthesis.</td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [12] and [13].

<sup>a</sup> Classified as aldehydes and vapor-phase agents.

<sup>b</sup> Classified as peroxygens and vapor-phase agents.
of a mycoylarabinogalactan-peptidoglycan skeleton that is covalently linked to a polysaccharide copolymer and of lipopolysaccharide, protein, and porin channels that allow migration of hydrophilic molecules. Cell wall components responsible for nonsusceptibility to biocides are unknown, but inhibitors of cell wall synthesis suggest that the cell wall acts as a permeability barrier to exclude hydrophilic biocides (e.g., chlorhexidine gluconate and quaternary ammonium compounds [QACs]) [15].

The basic strategy used by gram-negative bacteria to achieve nonsusceptibility is to decrease the accumulation of biocides within the cell by regulating or impairing their passage through the cell wall. The cell wall in gram-negative bacteria is composed of an inner membrane and associated efflux proteins, peptidoglycan, and a bilayered outer envelope composed of an outer membrane and lipopolysaccharides components. The outer membrane contains hydrophilic porin channels that regulate passage of solutes and is the primary barrier to the penetration of hydrophilic agents [16]. The lipopolysaccharide component is responsible for the impermeability of the outer membrane, and alterations to this component enhance the penetration of biocides [12]. In addition, changes in the outer membrane that affect the size of porins or alter the expression of porins to prevent penetration result in decreased susceptibility to hydrophobic biocides used as preservatives [3, 16].

Studies with triclosan have revealed the presence of a multidrug efflux pump that mediates nonsusceptibility to triclosan and to the household disinfectant pine oil [17–19]. In Escherichia coli, the Acr AB efflux pump, which belongs to the family of multidrug efflux systems known as resistance-nodulation-division, acts as a transporter of biocides and antibiotics. Up-regulation of the gene encoding the Acr AB efflux pump is mostly under control of the multiple antibiotic resistance activator (MarA). Environmental stimuli increase expression of MarA, resulting in elevated expression of the Acr AB efflux pump and nonsusceptibility. Disinfectants used in the hospital setting and in the home (such as pine oil) function as stimuli. Mutations in the gene encoding MarR, the multiple antibiotic resistance repressor, also allow expression of MarA and activation of the Acr AB efflux pump, resulting in reduced susceptibility to pine oil and to the hospital antiseptic triclosan [17, 20, 21]. Triclosan is also a substrate for multiple efflux pumps in Pseudomonas aeruginosa and selects for mutants that are nonsusceptible not only to triclosan but to clinically relevant antibiotics, such as ciprofloxacin [19].

Physiologic or phenotypic adaptation resulting in nonsusceptibility to biocides is usually manifested as a biofilm, especially in association with indwelling medical devices or contaminated medical products [22]. A biofilm is a community of sessile microorganisms that are irreversibly attached to a surface, are embedded in a polymeric extracellular matrix, and exhibit an altered growth rate [22]. Biocide nonsusceptibility in biofilms results from altered microbial growth rates that are attributable to nutrient depletion within the biofilm, binding of the biocide to the biofilm, and neutralization or degradation of the biocide. In addition, enzymatic degradation, or inactivation of biocides, has been reported when the concentrations of agents such as formaldehyde, chlorhexidine, and QACs are less than those used in clinical practice [7].

**Acquired nonsusceptibility.** Acquired nonsusceptibility to biocides occurs by means of mutation(s) at the target site, overexpression of the target, plasmid-mediated efflux, and enzymatic inactivation [3, 4, 12]. Studies of gram-negative bacteria describing changes in permeability that led to acquired biocide nonsusceptibility suggest the presence of mutations in the genes encoding for proteins in the outer membrane [21]. Phenotypic observations suggest that changes in the outer membrane fatty acid and protein composition, the ultrastructure, and the surface hydrophobicity are associated with acquired nonsusceptibility, although such changes have not been characterized at the genetic or molecular level [13, 22].

Some antiseptics have defined target sites [23, 24], and when mutations or hyperproduction of these sites occur, nonsusceptibility may develop [9, 25, 26]. The recently characterized mechanism of action of triclosan in E. coli shows that triclosan binds to enoyl-acyl protein reductase (Fab1), an enzyme involved in fatty acid synthesis [27]. A similar mechanism of action is described for strains of Mycobacterium smegmatis, in which missense mutations in the gene encoding enoyl reductase (InhA), a homologue of Fab1, are associated with decreased susceptibility to triclosan and cross-resistance to the antituberculosis drug isoniazid [28]. Conversely, isoniazid-resistant M. smegmatis strains are also nonsusceptible to triclosan, which confirms that emergence of resistance to one of these compounds counterselects resistance to the other.

Plasmid-mediated nonsusceptibility to cationic biocides, such as chlorhexidine gluconate and QACs, has been observed in staphylococci [6, 21]. Staphylococcus aureus isolates from clinical and food sources carry multidrug-resistant plasmids containing the qacA, qacB, qacC, and qacD genes, which encode multidrug efflux pumps that mediate biocide nonsusceptibility. Multidrug-resistant determinants in the qacA and qacB genes encode proton-dependent export proteins and have significant homology to other energy-dependent transporters found in association with tetracycline exporter–mediated resistance [9]. It is uncertain whether the modest levels of biocide nonsusceptibility provided by the efflux mechanism are clinically significant, because clinical failure due to this mechanism is practically unknown [21].
CONSEQUENCES OF REDUCED SUSCEPTIBILITY TO BIOCIDES

The nonsusceptibility of microorganisms to biocides and the targets that biocides share with antibiotics are of significant clinical interest. Two distinct issues have emerged from observations that some bacterial species showing nonsusceptibility to biocides may also demonstrate resistance to antibiotics.

The first issue is whether development of biocide nonsusceptibility by nosocomial pathogens, skin flora, and other microorganisms results in decreased clinical efficacy of biocides. Findings that triclosan inhibits the function of enoyl-acyl carrier protein (enoyl-ACP) reductase have led to concerns that bacteria may develop resistance to triclosan due to changes in triclosan’s affinity to this protein and to efflux-based mechanisms [18, 28]. In vitro susceptibility patterns of both clinical and community isolates of methicillin-susceptible S. aureus (MSSA), methicillin-resistant S. aureus (MRSA), and methicillin-susceptible or -resistant Staphylococcus epidermidis exhibit a combined MIC of ≤0.03–8.0 μg/mL, with a combined MIC<sub>50</sub> and MIC<sub>90</sub> of 0.12–2.0 and 0.25–8.0 μg/mL, respectively (table 3). Table 3 also shows that MRSA isolates demonstrate a higher triclosan MIC<sub>50</sub> and MIC<sub>90</sub> than do MSSA isolates [29, 32]. S. aureus isolates with a triclosan MIC of 1–2 μg/mL were shown to hyperexpress altered enoyl-ACP reductase [30].

Daily bathing of patients with triclosan-based agents also results in the selection of nonsusceptible MRSA (methicillin MIC, 2.0–4.0 μg/mL) [33]. Although in vitro susceptibility and genetic studies confirm that staphylococcal isolates have triclosan MICs higher than those for wild-type populations and contain mechanisms mediating triclosan nonsusceptibility, it is not clear whether such use selects for MRSA in the clinical setting; the importance of this finding remains unclear. Triclosan was used successfully to control an outbreak of MRSA infection and is recommended in conjunction with mupirocin for the eradication of MRSA nasal carriage [34, 35].

Biocides are used at very high concentrations, especially when included in disinfectants and sterilants. Biocide concentrations in skin antiseptics and preservatives, although low, are higher than most concentrations needed to demonstrate bacteriostatic and bactericidal effects on nonsusceptible vegetative pathogens. Although mechanisms resulting in nonsusceptibility to biocides have been observed in laboratory studies, evidence that intrinsic or acquired mechanisms of nonsusceptibility result in clinical failure has not emerged. However, contamination of a commercially available iodophor with P. aeruginosa that resulted in an outbreak of peritoneal infection was associated with a failed manufacturing process [36], and isolation of Serratia marcescens from benzalkonium chloride- and chlorhexidine gluconate-contaminated products that resulted in septic arthritis or nosocomial outbreaks of infection were associated with failed good laboratory practices [37, 38]. The mechanism leading to biocide nonsusceptibility appears to be biofilm formation, which is known to have significant clinical consequences [36, 38].

The second issue associated with reduced susceptibility to biocides is whether the emergence of biocide nonsusceptibility in microorganisms results in cross-resistance to clinically useful antibiotics [5–7]. There is concern that, as biocide concentrations decrease from their recommended use concentrations, these biocide gradients counterselect for nonsusceptible nosocomial pathogens. If the nonsusceptible organism is cross-resistant to an antibiotic, an undesirable outcome is created as a result of biocide use: selection of an antibiotic-resistant microorganism. Therefore, wide availability and use of antiseptics and the selection pressure associated with such use are of primary concern. If we accept this premise, the reciprocal argument that antibiotic resistance counterselects for biocide resistance is also true.

Clearly, nature is conservative and selects strategies that enhance the survival of living organisms. Therefore, it is not unreasonable to expect that existing survival strategies (such as those conferring antibiotic resistance) may be used in response to other toxic molecules (e.g., biocides) encountered by microorganisms. Published literature suggests that microorganisms have adopted the same adaptation strategies to deal with

<p>| Table 3. In vitro triclosan MICs for both clinical and community isolates of Staphylococcus aureus and Staphylococcus epidermidis. |</p>
<table>
<thead>
<tr>
<th>Staphylococcus species, no. of isolates tested (methicillin-susceptible/methicillin-resistant)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MIC, μg/mL</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;, μg/mL</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, μg/mL</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus (50/50)</td>
<td>0.06–4.0</td>
<td>0.12</td>
<td>0.25</td>
<td>[29]</td>
</tr>
<tr>
<td>S. epidermidis (49/47)</td>
<td>≤0.03–8.0</td>
<td>0.12</td>
<td>8.0</td>
<td>[29]</td>
</tr>
<tr>
<td>S. aureus (31)</td>
<td>0.016–2.0</td>
<td>0.16</td>
<td>1.0</td>
<td>[30]</td>
</tr>
<tr>
<td>S. aureus (50/50)</td>
<td>0.03–4.0</td>
<td>2.0</td>
<td>2.0</td>
<td>[31]</td>
</tr>
<tr>
<td>S. epidermidis (73)</td>
<td>0.03–4.0</td>
<td>0.125</td>
<td>2.0</td>
<td>[31]</td>
</tr>
<tr>
<td>S. aureus (0/232)</td>
<td>≤0.015–4.0</td>
<td>0.03</td>
<td>0.06</td>
<td>[32]</td>
</tr>
</tbody>
</table>

* Methicillin-susceptible and methicillin-resistant populations were tested. No single-value methicillin susceptibilities are described.
the toxic effects of antibiotics and biocides. For example, mechanisms that mediate resistance to antibiotics (i.e., changes at the target site, efflux, and impermeability) are the same strategies used to produce nonsusceptibility to biocides. Mutants of *M. smegmatis*, whether selected in the presence of the biocide triclosan or the antimicrobial isoniazid, showed cross-resistance via mutation of the *inhA* gene encoding enoyl-ACP reductase [28]. *P. aeruginosa*, a clinically significant pathogen intrinsically resistant to triclosan, hyperexpresses the MexCD-OprJ efflux pump because of mutations in the regulatory gene *nfxB* that controls expression of this pump. Hyperexpression resulted in multidrug-resistant bacteria that demonstrated increased nonsusceptibility to triclosan and clinically relevant resistance to erythromycin, tetracycline, and trimethoprim [19]. Ciprofloxacin MICs also increased 94-fold, from 0.064 to 0.75 μg/mL, but remained in the susceptible range. In addition, mechanisms mediating nonsusceptibility by means of efflux (which are encoded by *qacA–G*) are found on conjugative plasmids, and acquisition of plasmids by wild-type organisms is associated with the acquisition of biocide susceptibility traits [7]—the same evolutionary strategy used by bacteria to acquire and disseminate antibiotic-resistant determinants. From the perspective of the pathogen, the acquisition of plasmids mediating biocide nonsusceptibility and antibiotic resistance is a desirable survival strategy.

Plasmid-mediated resistance to biocides is extensively studied and best understood in staphylococci [39]. MRSA isolates resistant to gentamicin demonstrate elevated MICs of QACs and chlorhexidine [40]. Curing of plasmids resident in MRSA results in greater susceptibility to chlorhexidine, suggesting that chlorhexidine nonsusceptibility is plasmid mediated. Nonsusceptibility to QACs and chlorhexidine is associated with efflux mechanisms encoded by *qacA/B* and *qacC/D*; *qacA* is present in the genome of the pSK1 family of multidrug-resistant plasmids in *S. aureus* [6, 9, 21]. The clinical significance of these low-level mechanisms was explored via an in vivo skin test in which subjects were exposed to MSSA and MRSA that were nonsusceptible to biocides. No clinically significant differences in survival rates for MSSA and MRSA were seen after application of chlorhexidine, suggesting its potential effectiveness as a hand-washing agent for MRSA [40].

Parallels between nonsusceptibility to biocides and antibiotic resistance demonstrate that evolution is a conservative yet dynamic process, and when successful strategies evolve, microorganisms adopt these strategies to counter toxic environments. Thus, if antibiotic and antiseptic mechanisms of action are the same or if both types of antimicrobials are substrates for efflux pumps, cross-resistance is likely to occur. In addition, if determinants of biocide and antibiotic resistance are resident in the same host, then exposure to either agent counterselects for both resistance determinants. Investigation of the frequency and genetic linkage of QAC-based efflux and β-lactamase resistance in *Staphylococcus* species demonstrated that more than one-half of the species evaluated were nonsusceptible to the disinfectant benzalkonium chloride [41]. The *qacA/B* genes were found on the same plasmid that mediated resistance to β-lactams in 19 of 73 disinfectant-resistant strains. The investigators concluded that selection of either resistance determinant counterselected for the other.

The lack of scientific evidence to support the prevalent use of biocide-containing products in community environments and the consequences such uses have on the selection of microorganisms resistant to clinically important antibiotics is of concern. Laboratory studies demonstrating the potential for cross-resistance between antiseptics and some antibiotics prompted professional organizations to question the lack of proven infection-control benefit by antimicrobial-impregnated household products and the potential for the emergence of antiseptic-mediated resistance to useful antibiotics [42, 43]. Implied in this concern is the acknowledgment that biocides are important and critical components of the practice of medicine and within the health care community. The scientific community must assess the importance of biocides and weigh the risks of their use against the benefits they provide.

**CONCLUSION**

Biocides are integral and necessary components of the strategy to prevent dissemination of nosocomial infections in the clinical community, and their antimicrobial efficacy has been documented. However, unlike the mechanisms of action of antibiotics, those of biocides remain poorly characterized, especially at suboptimal concentrations. The published literature has described possible multiple targets of biocides when used in concentrations that have bactericidal effects. However, studies of suboptimal biocide concentrations are necessary to understand whether specific targets exist and the role such targets play in selection of resistance to important antibiotics. It may be possible to evaluate biocide susceptibility patterns of antibiotic-resistant organisms and then compare data for these isolates with data for the wild-type biocide-susceptible population. If antibiotic-resistant pathogens are shown to have elevated biocide susceptibility patterns, they may be cross-resistant and would provide an enriched population for further analysis.

By understanding the mechanisms of action of biocides, we gain insight into molecular mechanisms that result in biocide nonsusceptibility in microorganisms and the possible relationship of cross-resistance to antibiotics. Surveillance studies are needed to understand the prevalence of mechanisms of biocide nonsusceptibility in microbial communities. By incorporating into this investigation the same epidemiological tools used to monitor antibiotic resistance, we can make better risk/benefit
decisions about the implications of biocide use and the emergence of antibiotic resistance.

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References