Use of Germicides in the Home and the Healthcare Setting: Is There a Relationship Between Germicide Use and Antibiotic Resistance?

David J. Weber, MD, MPH; William A. Rutala, PhD, MPH

Background. The spread of antibiotic-resistant pathogens represents an increasing threat in healthcare facilities. Concern has been expressed that the use of surface disinfectants and antiseptics may select for antibiotic-resistant pathogens.

Objective. To review the scientific literature on whether there is a link between use of germicides (ie, disinfectants and antiseptics) and bacterial resistance to antibiotics. In addition, we will review whether antibiotic-resistant bacteria exhibit altered susceptibility to germicides that are recommended for use as disinfectants or antiseptics.

Design. A review of the appropriate scientific literature.

Results. In the laboratory, it has been possible to develop bacterial mutants with reduced susceptibility to disinfectants and antiseptics that also demonstrate decreased susceptibility to antibiotics. However, the antibiotic resistance described was not clinically relevant because the test organism was rarely a human pathogen, the altered level of antimicrobial susceptibility was within achievable serum levels for the antibiotic, or the antibiotic tested was not clinically used to treat the study pathogen. Similarly, wild-type strains with reduced susceptibility to disinfectants (principally, quaternary ammonium compounds) and antiseptics (principally, triclosan) have been reported. However, because the concentration of disinfectants used in the healthcare setting greatly exceeds the concentration required to kill strains with reduced susceptibility to disinfectants, the clinical relevance of these observations is questionable.

Conclusion. To date, there is no evidence that using recommended antiseptics or disinfectants selects for antibiotic-resistant organisms in nature. Disinfectants and antiseptics should be used when there are scientific studies demonstrating benefit or when there is a strong theoretical rationale for using germicides.
literature on the link between germicide use and resistance to antibiotics. In addition, we review whether antibiotic-resistant bacteria exhibit altered susceptibility to germicides recommended for use as disinfectants or antiseptics.

**Definitions**

A precise understanding of terminology is crucial to the evaluation of a putative link between germicide use and antibiotic resistance. Biocidal agents (also termed germicides), including antiseptics and disinfectants, inactivate microorganisms. Other agents designated by words with the suffix “-cide” (eg, virucide, fungicide, bactericide, sporicide, and tuberculocide) destroy the microorganisms identified by the prefix. Antiseptics are antimicrobial substances that are applied to the skin to reduce the number of microbial flora. Disinfectants are substances that are applied to inanimate objects to destroy harmful microorganisms, although they may not kill bacterial spores. This review will focus on antiseptics used in the United States (Table 1) and disinfectants that have been approved for use by the US Food and Drug Administration or registered by the US Environmental Protection Agency (Table 2). Disinfectants are further categorized by their degree of effectiveness. Disinfectants with high-level effectiveness inactivate all microorganisms, with the exception of high numbers of bacterial spores. Intermediate-level disinfectants inactivate *M. tuberculosis*, vegetative bacteria, and most viruses and fungi, but they do not necessarily kill bacterial spores. Low-level disinfectants kill most bacteria and some viruses and fungi, but they cannot be relied on to kill more-resistant microorganisms, such as tubercle bacilli or bacterial spores.

The main objective of susceptibility testing of antibiotics is to predict the outcome of treatment with the antibiotics tested. The minimum inhibitory concentration (MIC) is the fundamental measurement that forms the basis for most susceptibility testing methods. The implication of the “susceptible” category implies that an infection due to the strain being tested may be appropriately treated with the dosage of the antibiotic agent recommended for the type of infection and infecting species. The breakpoint for determining susceptibility is based principally on pharmacokinetic parameters and results of in vitro studies, animal studies, and human clinical trials. Many factors affect both the validity of the test (eg, composition of the medium, size of the inoculum, duration of incubation, and temperature) and the actual clinical efficacy of the therapy (eg, host defenses, site of infection, and presence of a foreign body or abscess). “Resistant” strains are not inhibited by the usual achievable systemic concentrations of the agent with normal dosage schedules and/or likely have specific microbial resistance mechanisms (eg, β-lactamases), and the clinical efficacy of agents to inhibit these strains has not been reliably demonstrated in treatment studies.

**Table 1. Antiseptic Agents Used in the United States**

<table>
<thead>
<tr>
<th>Agent (most commonly used dilution)</th>
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<tbody>
<tr>
<td>Alcohols (60%-95% ethanol, isopropanol)</td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine gluconate (0.5%-4%)</td>
<td></td>
</tr>
<tr>
<td>Parachlorometaxylenol (0.3%-3.75%)</td>
<td></td>
</tr>
<tr>
<td>Hexachlorophene (3%)</td>
<td></td>
</tr>
<tr>
<td>Iodine (1%) and iodophors (7.5%-10%)</td>
<td></td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td></td>
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<tr>
<td>Triclosan (0.2%-2%)</td>
<td></td>
</tr>
</tbody>
</table>

**Note.** Agents may be combined in some preparations. Data are from Boyce and Pittet.

**Table 2. Disinfectants Approved for Use in Healthcare Facilities in the United States**

<table>
<thead>
<tr>
<th>Disinfectant (dilution), by degree of effectiveness</th>
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<tbody>
<tr>
<td><strong>High level (cleared by US Food and Drug Administration)</strong></td>
<td></td>
</tr>
<tr>
<td>Glutaraldehyde (&gt;2%)</td>
<td></td>
</tr>
<tr>
<td>Glutaraldehyde (1.12%) and phenol/phenate (1.93%)</td>
<td></td>
</tr>
<tr>
<td>Ortho-phthalaldehyde (0.55%)</td>
<td></td>
</tr>
<tr>
<td>Hydrogen peroxide (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Hydrogen peroxide (7.35%) and peracetic acid (0.23%)</td>
<td></td>
</tr>
<tr>
<td>Hydrogen peroxide (1.0%) and peracetic acid (0.08%)</td>
<td></td>
</tr>
<tr>
<td>Hypochlorite (single-use chlorine generated by electrolyzing saline containing &gt;650-675 ppm of active free chlorine)</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate level (registered by the US Environmental Protection Agency)</strong></td>
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</tr>
<tr>
<td>Sodium hypochlorite (5.25%-6.15% household bleach diluted 1:100, ~500 ppm available chlorine)</td>
<td></td>
</tr>
<tr>
<td>Ethyl or isopropyl alcohol (70%-90%)</td>
<td></td>
</tr>
<tr>
<td>Phenolic (follow product label for use-dilution)</td>
<td></td>
</tr>
<tr>
<td><strong>Low level (registered by the US Environmental Protection Agency)</strong></td>
<td></td>
</tr>
<tr>
<td>Ethyl or isopropyl alcohol (70%-90%)</td>
<td></td>
</tr>
<tr>
<td>Sodium hypochlorite (5.25%-6.15% household bleach diluted 1:500, ~100 ppm available chlorine)</td>
<td></td>
</tr>
<tr>
<td>Phenolic (follow product label for use-dilution)</td>
<td></td>
</tr>
<tr>
<td>Quaternary ammonium germicidal detergent solution (follow product label for use-dilution)</td>
<td></td>
</tr>
<tr>
<td>Iodophor germicidal solution (follow product label for use-dilution)</td>
<td></td>
</tr>
</tbody>
</table>

**Note.** Data are from Rutala and Weber.
precise use in reference to antibiotic therapy, the term “resistant” has been loosely used when referring to activity of a germicide. Authors have described microbes that possess an elevated MIC to a germicide as “resistant” even though the microbe is inactivated by the germicide at its recommended use concentration. Thus the term “resistant” is incorrect when applied to pathogens exhibiting an elevated MIC to a germicide, and the accurate term is “reduced susceptibility” or “increased tolerance.”56,63,64 Heinzel65 has noted that most cases that are attributed by the user to resistance turn out to be episodes in which the disinfectant was misused, including (1) use of an inappropriate product (ie, the pathogen exhibits intrinsic resistance to the disinfectant); (2) application of the product without regard to proper duration, concentration, pH, or temperature; (3) failure to remove organic debris (ie, improper cleaning) prior to disinfection; (4) insufficient contact of the disinfectant with the surface to be treated; and (5) insufficient availability of the active product (eg, failure to use a proper dilution of an iodophor, because free iodine may be present in lower concentration in more concentrated products).

**Antibiotic Resistance**

Microbes may exhibit resistance to antibiotics66–68 via several broad mechanisms, including drug inactivation or modification,69–70 target-site alteration,71–75 development of bypass pathways,76 and altered intracellular concentration due to decreased permeability or enhanced efflux.73,74,77–79 Resistance may be intrinsic (ie, innate) or an acquired characteristic (ie, due to mutation or acquisition of plasmids or transposons). Resistant genes may reside on the chromosome, on a plasmid, or on a transposon. Multiple mechanisms may mediate resistance to specific antibiotics, such as trimethoprim–sulfamethoxazole69 or quinolones.81 Clinically important resistant organisms, such as drug-resistant *S. pneumoniae*,82,83 MRSA,84 and vancomycin-resistant enterococci (VRE),85 are more likely than susceptible strains to exhibit multidrug resistance.

**Resistance to Germicides**

Resistance to germicides has been reviewed elsewhere.69,86,87 As with antibiotic resistance, resistance to germicides may be an intrinsic or acquired property.83 Microbes exhibit a wide variation in intrinsic resistance to disinfectants (Table 3). This hierarchy is a general scheme; the relative resistance of individual microbes and, potentially, groups of microbes may vary depending on the specific class of disinfectants (ie, phenols, alcohols, and chlorine compounds). Intrinsic resistance is associated with constitutive degradative enzymes but is more commonly linked to cellular impermeability. Both mechanisms limit the concentration of the germicide to reach the target site(s) in microbes. Prions, the agents most resistant to germicides, are not inactivated by any of the commonly used high-level hospital disinfectants.85 Coccidial cysts (eg, *Cryptosporidium parvum*) are also resistant to most hospital high-level disinfectants used to reprocess medical devices, such as endoscopes.86 As with antibiotic resistance, resistance to germicides may be encoded on plasmids.97,98 Germicide resistance is mediated by mechanisms similar to those that mediate antibiotic resistance, including drug inactivation or modification, target-site alteration, and altered intracellular concentration due to decreased permeability or enhanced efflux. Importantly, acquired resistance to high-level disinfectants (eg, hydrogen peroxide, glutaraldehyde, chlorine, and alcohol) at concentrations used for high-level disinfection has not been described.

**Inactivation of Antibiotic-Resistant Bacteria by Disinfectants**

Several investigators have analyzed MICs to assess the susceptibility of antibiotic-resistant pathogens to disinfectants.99–101 Al-Masaudi et al.99 reported that MRSA and methicillin-susceptible *S. aureus* (MSSA) strains were both susceptible to phenols and chlorhexidine but slightly (2–4 times) less susceptible to quaternary ammonium compounds. Subsequent work by these investigators that involved other strains of *S. aureus* confirmed that MRSA strains were slightly less susceptible to quaternary ammonium compounds.103 Other investigators have reported that MRSA exhibited 5–10 times higher MICs to chlorhexidine, compared with MSSA strains.103 Similarly, drug-resistant enterococci exhibited similar susceptibility to phenols but “greater variation” in susceptibility to

<table>
<thead>
<tr>
<th>Table 3. Hierarchy of Relative Resistance to Germicides Among Microbial Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microbial class (example organism[s])</strong></td>
</tr>
<tr>
<td>Bacterial spores (<em>Bacillus atrophaeus</em>)</td>
</tr>
<tr>
<td>Coccidia (<em>Cryptosporidium</em> species)</td>
</tr>
<tr>
<td>Mycobacteria (<em>Mycobacterium tuberculosis</em> and <em>Mycobacterium terrae</em>)</td>
</tr>
<tr>
<td>Nonlipid or small viruses (poliovirus, coxsackievirus)</td>
</tr>
<tr>
<td>Fungi (<em>Aspergillus</em> species and <em>Candida</em> species)</td>
</tr>
<tr>
<td>Vegetative bacteria (<em>Staphylococcus aureus</em> and <em>Pseudomonas aeruginosa</em>)</td>
</tr>
<tr>
<td>Lipid or medium-sized viruses (HIV, herpesvirus, hepatitis B virus)</td>
</tr>
</tbody>
</table>

**Note.** Microbial classes are ranked from the least susceptible (top) to the most susceptible (bottom) to germicides. HIV, human immunodeficiency virus. Data are modified from findings reported by Maillard.94
chlorhexidine and quaternary ammonium compounds. Other investigators have also failed to demonstrate reduced susceptibility of VRE to disinfectants, including a chlorine-releasing agent, an alcohol, and a glutaraldehyde product. Kuchen et al. assessed clinical isolates of several multiantibiotic-resistant gram-negative bacteria and reported that the susceptibility of these strains to quaternary ammonium compounds was similar to that of antibiotic-susceptible strains. However, Koljalg et al. reported that some clinical isolates of gram-negative bacteria that exhibited resistance to several antibiotics (e.g., imipenem, ceftriaxone, and ciprofloxacin) exhibited increased tolerance to chlorhexidine. Sakagami and Kajimura assessed the bactericidal activities of 35 commercially available disinfectants and reported no differences in bactericidal time for activity against VRE versus vancomycin-susceptible enterococci (VSE). Disinfectant classes tested included alcohols, aldehydes, iodine compounds, cation surfactant and amphoteric compounds, and biguanide-containing agents. Importantly, strains of antibiotic-resistant pathogens demonstrating slightly reduced susceptibility to germicides were readily inactivated at concentrations of germicides commonly used in the healthcare setting.

The susceptibility of antibiotic-resistant pathogens to surface disinfectants used at the appropriate dilution (i.e., use dilution) has also been investigated. Anderson et al. reported that VRE strains were more susceptible than VSE strains to the use dilutions of quaternary ammonium, phenolic, or iodophor germicides. Even when germicides were diluted below the level of their recommended use dilution, antibiotic-resistant pathogens did not demonstrate reduced susceptibility to germicides. Rutala and colleagues reported that resistant and susceptible strains of S. aureus, S. epidermidis, E. coli, K. pneumoniae, P. aeruginosa, Enterococcus species, and S. choleraesuis demonstrated similar susceptibilities to a phenolic compound and a quaternary ammonium compound.

In addition, the susceptibility of VRE and MRSA to a variety of surface disinfectants (such as phenolics, quaternary ammonium compound, and sodium hypochlorite) has been assessed in time-kill experiments. VRE was completely inactivated in 15 seconds by all disinfectants. MRSA was inactivated in 15-30 seconds with 10% bleach and Vesphe nenllse (Steris), whereas Lysol products (Reckitt Benckiser) demonstrated inactivation in 30-60 seconds. The susceptibilities of antibiotic-resistant and antibiotic-susceptible bacteria to germicides are summarized in Table 4.

### Table 4. Germicide Susceptibility Among Antibiotic-Resistant and Antibiotic-Susceptible Bacteria

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bacteria</th>
<th>Effect of antibiotic resistance and susceptibility on susceptibility to germicides</th>
<th>Reduced susceptibility</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>al-Masaudi et al., 1988</td>
<td>MRSA</td>
<td>Phenols, chlorhexidine</td>
<td>QACs</td>
<td>None</td>
</tr>
<tr>
<td>al-Masaudi et al., 1991</td>
<td>MRSA</td>
<td>Phenols, chlorhexidine</td>
<td>QACs</td>
<td>None</td>
</tr>
<tr>
<td>Bradley and Fraise, 1996</td>
<td>VRE</td>
<td>Chlorine, alcohol, glutaraldehyde</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Anderson et al., 1997</td>
<td>VRE</td>
<td>Phenol, QAC, iodophor</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rutala et al., 1997</td>
<td>MRSA, VRE</td>
<td>Phenol, QAC</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Koljalg et al., 2002</td>
<td>GNR</td>
<td>...</td>
<td>Chlorhexidine</td>
<td>None</td>
</tr>
<tr>
<td>Sakagami and Kajimura, 2002</td>
<td>VRE</td>
<td>Aldehydes, alcohols, iodine compounds, cation surfactant and amphoteric compounds, agents from the biguanide group</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Note.** GNR, gram-negative bacilli resistant to imipenem, ceftazidime, cefotaxime, aztreonam, gentamicin, or ciprofloxacin; MRSA, methicillin-resistant *Staphylococcus aureus*; QAC, quaternary ammonium compounds; VRE, vancomycin-resistant enterococci.

In the laboratory, it has been possible to develop mutants with reduced susceptibility to germicides that demonstrate decreased susceptibility or resistance to antibiotics (Table 5). Moken et al. exposed *E. coli* to sublethal concentrations of pine oil, which led to selection of a strain that demonstrated resistance to pine oil and decreased susceptibility to tetacycline, ampicillin, and chloramphenicol. The mechanism of resistance was likely enhanced efflux. Similarly, Price and coworkers reported that pine oil–resistant *S. aureus* demonstrated a reduced susceptibility to vancomycin (MIC, ≥1 μg/mL). Russell et al. developed stable chlorhexidine resistance in some strains of *Pseudomonas stutzeri* by exposing the organisms to increasing concentrations of biguanides. The chlorhexidine-resistant strains showed a variable reduced susceptibility to quaternary ammonium compounds, triclocan, polymyxin B, gentamicin, nalidixic acid, erythromycin, and ampicillin. Akimitsu and coworkers isolated an MRSA mutant with a 2-fold–reduced susceptibility to benzalkonium chloride whose MIC for oxacillin was 8-fold greater than that for the parent strain. Brown and Tomlinson selected for strains of *P. aeruginosa* with polymyxin resistance and showed that such strains developed decreased susceptibility to quaternary ammonium compounds resistant to chlorhexidine and quaternary ammonium compounds.
**Table 5.** Laboratory-Developed Pathogen Strains with Germicide-Linked Antimicrobial Resistance

<table>
<thead>
<tr>
<th>Reference</th>
<th>Test organism</th>
<th>Agent</th>
<th>MIC, µg/mL</th>
<th>Gene affected</th>
<th>Agent</th>
<th>MIC, µg/mL</th>
<th>Clinically significant difference in MIC&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moken et al.,&lt;sup&gt;1,11&lt;/sup&gt; 1997</td>
<td><em>E. coli</em></td>
<td>Pine oil</td>
<td>0.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Ampicillin</td>
<td>&lt;1.2</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;4.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Tetracycline</td>
<td>1.8</td>
<td>&gt;12.8</td>
</tr>
<tr>
<td>Russell et al.,&lt;sup&gt;1,12&lt;/sup&gt; 1998</td>
<td><em>P. stutzeri</em></td>
<td>Chlorhexidine</td>
<td>2.5 to 5</td>
<td></td>
<td>Chloramphenicol</td>
<td>2.6</td>
<td>&gt;35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 to 100</td>
<td></td>
<td>Triclosan</td>
<td>1</td>
<td>1 to 250</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polymyxin B</td>
<td>&lt;1</td>
<td>&lt;1 to &gt;500</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gentamicin</td>
<td>25 to 50</td>
<td>5 to &gt;200</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Erythromycin</td>
<td>1</td>
<td>1 to 250</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ampicillin</td>
<td>10 to 100</td>
<td>100 to &gt;500</td>
</tr>
<tr>
<td>Akimitsu et al.,&lt;sup&gt;1,13&lt;/sup&gt; 1999</td>
<td>MRSA</td>
<td>Benzalkonium chloride</td>
<td>5</td>
<td></td>
<td>Oxacillin</td>
<td>16</td>
<td>64 to 512</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td>Ampicillin</td>
<td>16</td>
<td>16 to 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cefazolin</td>
<td>64</td>
<td>64 to 128</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ofloxacin</td>
<td>8</td>
<td>16 to 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tetracycline</td>
<td>125</td>
<td>32 to 128</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kanamycin</td>
<td>256</td>
<td>256 to 512</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Chloramphenicol</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Chuanchuen et al.,&lt;sup&gt;1,17&lt;/sup&gt; 2001</td>
<td><em>P. aeruginosa</em></td>
<td>Triclosan</td>
<td>24</td>
<td>&gt;128</td>
<td>NfxB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McMurry et al.,&lt;sup&gt;1,16&lt;/sup&gt; 1999</td>
<td><em>M. smegmatis</em></td>
<td>Triclosan</td>
<td>1.0</td>
<td>4.0 to 6.3</td>
<td>IImA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tattawasart et al.,&lt;sup&gt;1,14&lt;/sup&gt; 1999</td>
<td><em>P. stutzeri</em></td>
<td>Chlorhexidine diacetate</td>
<td>1 to 2.5</td>
<td>25 to 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tattawasart et al.,&lt;sup&gt;1,14&lt;/sup&gt; 1999</td>
<td><em>P. aeruginosa</em></td>
<td>Chlorhexidine diacetate</td>
<td>10</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note.** No standard means that the organism is intrinsically resistant or the antimicrobial is not used clinically. *E. coli*, *Escherichia coli*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; *M. smegmatis*, *Mycobacterium smegmatis*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *P. stutzeri*, *Pseudomonas stutzeri*.

<sup>a</sup> Clinically significant increase in MIC from a clinically achievable MIC to an MIC unachievable in humans (ie, the MIC increased from the susceptible range to the resistant range, as defined by NCCLS criteria<sup>16</sup>).

<sup>b</sup> Data are percent weight by volume.
ternary ammonium compounds. Importantly, investigations of laboratory-induced cross-resistance have frequently tested antibiotics that are of limited or no clinical relevance, because even control strains exhibited innate resistance at clinically relevant concentrations based on Clinical and Laboratory Standards Institute breakpoints (Table 5). Clinically relevant resistance was only occasionally demonstrated, and when present, involved antibiotics of limited current use (eg, chloramphenicol resistance in *E. coli* and tetracycline resistance in *P. aeruginosa*). Multidrug resistance was not demonstrated.

Laboratory-induced resistance to a germicide has also been reported to lead to increased susceptibility to antibiotics. For example, Adair and colleagues generated mutants of *P. aeruginosa* with decreased susceptibility to benzalkonium chloride; such mutants had stable susceptibility to gentamicin and rifampin but increased susceptibility to polymyxin B and colistin.

## Acquired Tolerance to Germicides

Acquired tolerance to disinfectants or antiseptics has been reported for only a limited number of agents. The use of chlorhexidine for bladder washes (concentration, <1 µg/mL) has been associated with urinary tract infection due to gram-negative bacilli, especially *Proteus mirabilis*, which has been shown to be resistant to chlorhexidine at a concentration of more than 800 µg/mL. However, chlorhexidine is usually used in the hospital at a concentration of 2%–4% (20,000–40,000 µg/mL). Plasmid-mediated resistance to silver, other metals, and organomercurials have been extensively investigated. More recently, there have been multiple reports linking the presence of plasmids in bacteria with increased tolerance to chlorhexidine, quaternary ammonium compounds, and triclosan.

Staphylococci are the only bacteria in which the genetic aspects of plasmid-mediated antiseptic and disinfectant-resistant mechanisms have been described. Decreased susceptibility to chlorhexidine and quaternary ammonium compounds has been reported to be widespread among MRSA strains. Tolerance is mediated by the *qac* family of genes that code for proton-dependent export proteins involved in an efflux system that actively reduces intracellular accumulation of toxicants, such as quaternary ammonium compounds.

Strains carrying *qac* genes may exhibit reduced susceptibility to aminoglycosides and/or tetracycline. Coagulase-negative staphylococci frequently also contain *qac* genes. Studies have established that the *qac* genes consist of 2 gene families, *qacCD* (now referred to as *smr*) and *gacAB*.

Triclosan is a synthetic, nonionic, broad-spectrum antibacterial and antifungal agent. Strains of *E. coli* with reduced susceptibility to triclosan have been developed in the laboratory as a result of mutations in the *FabI* gene. The *FabI* gene of *E. coli* encodes the enoyl-acyl carrier protein reductase, which catalyzes a necessary step in fatty acid biosynthesis. Other investigators have confirmed that *FabI* gene mutations in *E. coli* result in decreased tolerance to triclosan. It is now known that triclosan targets a specific bacterial fatty acid biosynthetic enzyme, enoyl [acyl-carrier protein]–reductase, that is present in gram-negative bacteria, gram-positive bacteria, and mycobacteria. For example, enoyl-reductase targets have been found in *S. aureus*, *S. pneumoniae*, *P. aeruginosa*, and *M. tuberculosis*. Decreased susceptibility to triclosan has been reported in clinical specimens of *S. aureus*. However, strains with reduced susceptibility to triclosan were not more likely to demonstrate resistance to methicillin or other antibiotics. Investigators have also reported increased tolerance to triclosan due to mutations in efflux pumps of *E. coli* and *P. aeruginosa*. In addition, increased tolerance to triclosan was produced with *Mycobacterium smegmatis*, and such strains demonstrated increased tolerance of isoniazid. Although enoyl-reductase is also found in *M. tuberculosis*, the clinical relevance of developing strains in the laboratory with increased tolerance of isoniazid is unclear, because *M. tuberculosis* is transmitted via airborne spread from person to person (ie, without an opportunity to come into contact with a germicide, such as triclosan). Triclosan formulations have been used either as personnel handwashing agents or as patient bathing agents to control endemic and epidemic MRSA and outbreaks of *Clostridium difficile* infection.

## Issues in the Incorporation of a Germicide (Triclosan) Into Home Products

Multiple home and personal-care products have recently been produced that contain triclosan, including underarm deodorants, soaps, oral rinses, toothpaste, and cutting boards. For example, in one survey, triclosan was found to be present in 76% of liquid soaps and 29% of bar soaps. No data support the efficacy of these products in reducing the incidence of infection in the home setting. Testing of triclosan-impregnated storage boxes in simulated domestic use did not demonstrate evidence that several bacterial species would develop resistance, including *S. aureus*, *E. coli*, *P. aeruginosa*, *Bacillus cereus*, and *Shewanella putrefaciens*. More recently, a randomized home hygiene intervention in which a liquid soap containing 0.2% triclosan was provided to subjects in the intervention arm and a similar product without triclosan was provided to subjects in the control arm did not demonstrate a statistical change in bacterial resistances among staphylococci or gram-negative bacilli isolated from the hands of study subjects. However, the impact of widespread use on promoting either resistance to disinfectants or antibiotics has not been evaluated. The Association for Professionals in Infection Control and Epidemiology (APIC) has published a position paper that states that "APIC does not advocate the use of antimicrobial household products which are marketed with the implication of preventing infection."
**Disinfection and Antisepsis in Healthcare Facilities**

Healthcare-associated infections continue to be an important cause of morbidity and mortality in the United States. Each year, approximately 2 million persons develop a healthcare-associated infection, leading to approximately 88,000 deaths. Disinfection and antisepsis recommendations based on findings from multiple scientific studies are key interventions in preventing healthcare-associated infection. The scheme first proposed by Spaulding forms the basis for current disinfection recommendations. Critical items, defined as medical devices that enter sterile tissue (eg, surgical instruments) and implants (eg, prosthetic heart valves), should be sterilized prior to use. Semicritical items, defined as medical devices that come into contact with nonintact skin or mucous membranes (eg, bronchoscopes), should minimally undergo high-level disinfection prior to use. Noncritical items, defined as objects that may contact intact skin (eg, blood pressure cuffs), should receive low-level disinfection prior to use. Some authors have divided noncritical items into items that may have contact with intact skin (eg, bed rails and blood pressure cuffs) and environmental surfaces that do not have contact with skin (eg, floors and walls).

Failure to sterilize critical items has led to serious infections. For example, outbreaks of nosocomial infections have been traced to contaminated prosthetic heart valves and intraocular lenses. Similarly, failure to adhere to guidelines for high-level disinfection of semicritical items, especially endoscopes, has led to multiple nosocomial outbreaks. More than 10 outbreaks and 30 pseudo-outbreaks have been related to inadequately disinfected bronchoscopes, and more than 30 outbreaks have been related to inadequately disinfected gastrointestinal endoscopes. The impact of contamination of environmental surfaces with pathogenic organisms in the hospital setting has been more difficult to evaluate. Contamination of the environment in the vicinity of patients colonized or infected with MRSA, VRE, C. difficile, and gram-negative bacilli. Similarly, many studies have demonstrated the efficacy of antiseptics for elimination of such transient flora and reduction of overall bacterial counts. Quasi-experimental studies have demonstrated that hand hygiene is associated with a reduction in nosocomial infections. More recently, a large before-and-after intervention study reported that improved hand hygiene was associated with a significant reduction in the incidence of nosocomial infection and MRSA transmission. However, in addition to improved hand hygiene, several other interventions were undertaken, including one involving an increase in active surveillance to detect colonized patients for placement in contact precautions.

Despite the widespread use of disinfectants and antiseptics in hospitals, acquired resistance to current disinfectants has rarely been reported. For example, Klossner and colleagues evaluated 40 patients undergoing continuous ambulatory peritoneal dialysis and demonstrated that, despite the use of povidone-iodine for at least 6 months, povidone-resistant coagulase-negative staphylococci could not be isolated. Dance and colleagues reported an outbreak due to a chlorhexidine- and antibiotic-resistant strain of P. mirabilis, but their study suggested no genetic link between chlorhexidine use and resistance to multiple antibiotics. Similarly, linked resistance to germicides and antibiotics has rarely been observed.

**Disinfection in the Home**

The level and type of microbial contamination of environmental surfaces in the home have been carefully studied. The highest levels of bacterial contamination were found on surfaces in the kitchen and bathroom. Environmental surveys have discovered contamination with potential pathogens, such as Salmonella species, Listeria species, Yersinia enterocolitica, P. aeruginosa, and enteric gram-negative bacilli. In a study of household transmission of E. coli O157:H7, it was shown that the transmission rate of spread was 4%-15%. More recently, it has been shown that several environmental...
surfaces in the home, rather than improperly cooked food, were sources of Salmonella infections in children.184 However, human illness related to ingestion of contaminated food is increasingly appreciated as a problem of major public health concern.187,188 It is estimated that foodborne disease causes approximately 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths in the United States each year.188 The impact of contaminated environmental surfaces in the home on the incidence of foodborne human illness has not been defined. Similarly, the role of contaminated environmental surfaces in the bathroom on human disease has not been studied. The use of antimicrobial cleaners (eg, those containing hypochlorite) has been demonstrated to lead to a significant reduction of bacteria in kitchens and bathrooms.184 It is also known from laboratory studies that many commercially prepared household disinfectants are effective against common pathogens110 and can interrupt surface-to-human transmission of pathogens such as rotavirus.190 The impact of hand carriage and antisepsis on transmission of viral respiratory disease along with the effectiveness of using antimicrobial soaps in reducing human illness in the home setting have not been studied. The importance of home hygiene has been reviewed in a recent symposium.190

In an observational study that evaluated selected potentially pathogenic bacteria for antibiotic resistance and the relationship between the prevalence of antibiotic resistance among isolates and the frequency of disinfectant use in the home, the investigators found no relationship between antibiotic resistance and the frequency of antibacterial use or the frequency of cleaning or disinfection.183 In a randomized trial, environmental and clinical samples were collected from the homes of antibacterial product users and nonusers for the isolation of target bacteria for susceptibility testing. The results showed a lack of antibiotic and antibacterial agent cross-resistance in target bacteria recovered from the homes of antibacterial product users and nonusers, as well as an increased prevalence of target organisms in nonuser homes.191

**Discussion**

Antibiotic-resistant pathogens represent a growing threat both in the community and the hospital. The main driving force for the development of resistance is the use (and overuse) of antibiotics. Intrinsic resistance of microbes to currently used disinfectants and antiseptics varies widely, mainly because of differences in permeability of the outer membrane barrier to the agents. Thus, bacterial spores tend to be the most resistant microbes, followed by mycobacteria. Tolerance of germicides is much less common than tolerance of antibiotics and reflects the multiplicity of targets within the cell as well as the general lack of known detoxifying enzymes. For example, chlorine is a strong oxidizing agent, and inactivation by chlorine may result from a variety of factors, such as oxidation of sulfhydryl groups and amino acids, ring chlorination of amino acids, loss of intracellular contents, inhibition of protein synthesis, and depressed DNA synthesis.64

Although chlorine has been used for more than 100 years to purify water, clinically relevant resistance to chlorine has not developed in any microbe.64,192 Whenever germicides are used, microbes are exposed to sublethal concentrations of the germicide as it becomes dissipated or diluted. The impact of such exposures at the molecular level or the relation of such exposures to the development of microbes with reduced susceptibility to either germicides or antimicrobials is unknown.

Acquired resistance to germicides has rarely been described in microbes isolated from clinical specimens or the environment. However, in all cases, clinical isolates with reduced susceptibility have remained susceptible to clinically used concentrations of the germicide. We are unaware of any example in which acquired resistance to currently used germicides has been described in a microbe, such that, over time, the proportion of resistant microbes has increased, rendering the germicide clinically ineffective. This stands in stark contrast to antibiotic resistance, in which widespread resistance has emerged over time, rendering a number of antibiotics without clinical value (eg, as found with penicillin and methicillin resistance in S. aureus and vancomycin resistance in enterococci).

In the laboratory, it is has been possible to develop mutants with reduced susceptibility to disinfectants and antiseptics. Similarly, wild-type strains with reduced susceptibility to disinfectants (principally quaternary ammonium compounds) and antiseptics (principally triclosan) have been reported. However, because the concentrations of disinfectants used in practice greatly exceed the MICs observed, even for the more tolerant strains, the clinical relevance of these observations is questionable. For example, although in the laboratory, strains with reduced susceptibility to triclosan have been developed, the MICs of triclosan-tolerant strains were generally low (ie, 1-25 μg/mL) and dissimilar to the higher levels of triclosan used in antimicrobial products (2,000-20,000 μg/mL). One study that found that soap containing triclosan may be less effective in inactivating bacteria produced laboratory strains tolerant of levels of triclosan (300-600 μg/mL) just below that contained in soap preparations.51

The link between germicide and antibiotic resistance has most commonly been studied in the laboratory by the selection of bacteria with decreased susceptibility to triclosan. Such strains may demonstrate decreased susceptibility to both germicides (eg, chlorhexidine and quaternary ammonium compounds) and antibiotics (eg, tetracycline). In general, these strains are susceptible to triclosan at commonly used concentrations. However, strains with reduced susceptibility may be difficult or impossible to eliminate by use of soap containing triclosan.51 Furthermore, many of the antibiotics tested are either not used clinically (eg, nalidixic acid) or not recommended for the pathogen studied, or the organism did not develop clinically relevant resistance (ie, an MIC greater than that could be clinically obtained in serum). Despite
the use of triclosan for more than 30 years, triclosan-resistant pathogens have not been isolated from the environment or normal human flora.

The issue of whether low-level tolerance of germicides leads to emergence of antibiotic-resistant strains is unsettled, but it may depend on the mechanism by which tolerance is attained. For example, changes in the permeability barrier or efflux mechanisms may affect susceptibility to antibiotics and germicides, but specific changes to a target site may not. To date, there is no evidence that use of antiseptics and disinfectants selects for antibiotic-resistant organisms in nature or that mutants survive in nature. In addition, there are fundamental differences between the actions of antibiotics and disinfectants. Antibiotics are selectively toxic and generally have a single target site in bacteria, thereby inhibiting a specific biosynthetic process. Germicides generally are considered to be nonspecific antimicrobials because of a multiplicity of toxic-effect mechanisms or target sites and have a broader spectrum of types of microorganisms against which they are effective.94,193

We believe that disinfectants and antiseptics should only be used when there are scientific studies demonstrating benefit or there is a strong theoretical reason for using these chemicals. We agree that home hygiene policies should be based on the concept of risk assessment.92,194 On the basis of this approach, critical risk situations can be identified and appropriate hygiene procedures applied to reduce risk. Risk depends on the frequency of the hazard, level of exposure and sensitivity to the hazard, consumer awareness of the hazard, and consumer knowledge of the threat to health posed by the hazard.187 Reduction of risk may involve cleaning with soap and water or disinfection with a commercial germicide. For example, there is general agreement that disinfectants (eg, chlorine, alcohol, and hydrogen peroxide) should be used to remove disease-causing bacteria from objects in contact with raw food (eg, utensils used to prepare raw meat for cooking). Current guidelines for the use of disinfectants and antiseptics in the hospital are evidence based and should be followed.57-59 Limited data are available on which to assess the benefits of disinfectants or antiseptics in the home. It may be reasonable to use disinfectants on environmental surfaces in the kitchen (eg, cutting boards and counters) that come into contact with food or surfaces in the bathroom that come into contact with the skin, especially the hands.

The appropriate use of germicides in the home, child care centers, and hospitals can significantly impact health by reducing the number of infections.57-59,195 Examples of appropriate hygiene include preparation of food, hand washing, hygiene associated with protection of high-risk patients, and hygiene after fecal or pet contamination. By reducing infection in these settings, we will reduce the need for antibiotic therapy and, hence, the main selective pressure for the development of antibiotic-resistant pathogens.196

Additional research should be undertaken to assess the advantages and disadvantages of the use of disinfectants in the home. Future recommendations should be based on these studies. Finally, continued research on the interrelationship of germicide use and the emergence of antimicrobial resistance mechanisms should be supported.

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ACKNOWLEDGMENT

The development of this article was supported, in part, by the Consumer Specialty Products Association.

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