

REVIEW ARTICLE

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

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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.

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The increasing frequency of resistance among human pathogens to antimicrobials has been recognized as a problem of major public health importance.¹⁻⁷ Pathogens of major concern that are predominantly acquired in the community include multidrug-resistant *Streptococcus pneumoniae*,⁸⁻¹² multidrug-resistant *Mycobacterium tuberculosis*,¹³⁻¹⁷ multidrug-resistant *Neisseria gonorrhoea*,¹⁸⁻²¹ multidrug-resistant *Salmonella* species,²²⁻²⁵ and community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).²⁶⁻²⁸ Hospital-acquired pathogens of major concern include MRSA,²⁹⁻³¹ vancomycin-resistant *Enterococcus* species,³²⁻³⁶ extended spectrum β -lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*,³⁷⁻⁴⁰ multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species,⁴¹⁻⁴⁵ and multidrug-resistant *M. tuberculosis*.^{46,47}

Factors reported to be driving the increased resistance among pathogens principally acquired in the community include frequent use (and overuse) of antibiotics by both healthcare professionals and patients, widespread use of an-

tibiotics in agriculture and animal production, patient non-compliance with antibiotic therapy, prolonged survival of persons with chronic diseases and altered host defenses, and increased populations in congregate settings (eg, prisons, jails, child care centers, and extended care facilities).⁴⁸ Factors reported to be driving the increased drug resistance among pathogens principally acquired in the hospital include greater severity of illness in hospitalized patients, presence of more severely immunocompromised patients, increased introduction of resistant pathogens from the community, effective implementation of infection control and isolation practices and compliance, increased use of antimicrobial prophylaxis, increased use of empirical polymicrobial therapy, and a high rate of antimicrobial use per geographic area per unit time.⁴⁹

Chemical germicides are widely used as antiseptics and disinfectants. Concern has been raised that the use of germicides contributes to development of antibiotic resistance among microbes.⁵⁰⁻⁵⁶ In this article, we review the scientific

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TABLE 1. Antiseptic Agents Used in the United States

Agent (most commonly used dilution)
Alcohols (60%-95% ethanol, isopropanol)
Chlorhexidine gluconate (0.5%-4%)
Parachlorometaxyleneol (0.3%-3.75%)
Hexachlorophene (3%)
Iodine (1%) and iodophors (7.5%-10%)
Benzalkonium chloride
Triclosan (0.2%-2%)

NOTE. Agents may be combined in some preparations. Data are from Boyce and Pittet.⁵⁹

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^{57,58} or antiseptics.⁵⁹

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 States⁵⁹ (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^{57,58} (Table 2). Disinfectants are further categorized by their degree of effectiveness.^{58,60} 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.⁶¹ The minimum inhibitory concentration (MIC) is the fundamental measurement that forms the basis for most susceptibility testing methods.⁶¹ 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.⁶² 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.⁶² In contrast to its

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

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

NOTE. Data are from Rutala and Weber.^{57,58}

TABLE 3. Hierarchy of Relative Resistance to Germicides Among Microbial Classes

Microbial class (example organism[s])
Bacterial spores (<i>Bacillus atrophaeus</i>)
Coccidia (<i>Cryptosporidium</i> species)
Mycobacteria (<i>Mycobacterium tuberculosis</i> and <i>Mycobacterium terrae</i>)
Nonlipid or small viruses (poliovirus, coxsackievirus)
Fungi (<i>Aspergillus</i> species and <i>Candida</i> species)
Vegetative bacteria (<i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i>)
Lipid or medium-sized viruses (HIV, herpesvirus, hepatitis B virus)

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

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} Heinzl⁶⁵ 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-sulfamethoxazole⁸⁰ or quinolones.⁸¹ Clinically important resistant pathogens, 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.^{63,64,86-92} As with antibiotic resistance, resistance to germicides may be

an intrinsic or acquired property.⁹³ 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.⁹⁵ Coccidial cysts (eg, *Cryptosporidium parvum*) are also resistant to most hospital high-level disinfectants used to reprocess medical devices, such as endoscopes.⁹⁶ 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.⁹⁹⁻¹⁰² Al-Masuadi 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.¹⁰⁰ 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 4. Germicide Susceptibility Among Antibiotic-Resistant and Antibiotic-Susceptible Bacteria

Reference	Bacteria	Effect of antibiotic resistance and susceptibility on susceptibility to germicides		
		No effect	Reduced susceptibility	Resistance
al-Masaudi et al., ⁹⁹ 1988	MRSA	Phenols, chlorhexidine	QACs	None
al-Masaudi et al., ¹⁰⁰ 1991	MRSA	...	QACs	None
Bradley and Fraise, ¹⁰⁴ 1996	VRE	Chlorine, alcohol, glutaraldehyde	None	None
Anderson et al., ¹⁰⁷ 1997	VRE	Phenol, QAC, iodophor	None	None
Rutala et al., ¹⁰⁸ 1997	MRSA, VRE	Phenol, QAC	None	None
Koljalg et al., ¹⁰⁵ 2002	GNR	...	Chlorhexidine	None
Sakagami and Kajimura, ¹⁰⁶ 2002	VRE	Aldehydes, alcohols, iodine compounds, cation surfactant and amphoteric compounds, agents from the biguanide group	None	None

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.

chlorhexidine and quaternary ammonium compounds.¹⁰¹ Other investigators have also failed to demonstrate reduced susceptibility of VRE to disinfectants, including a chlorine-releasing agent, an alcohol, and a glutaraldehyde product.¹⁰⁴ Kuchen et al.¹⁰² 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.¹⁰⁵ reported that some clinical isolates of gram-negative bacteria that exhibited resistance to several antibiotics (eg, imipenem, ceftriaxone, and ciprofloxacin) exhibited increased tolerance to chlorhexidine. Sakagami and Kajimura¹⁰⁶ 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 (ie, use dilution) has also been investigated.^{107,108} Anderson et al.¹⁰⁷ 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 colleagues¹⁰⁸ 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 va-

riety of surface disinfectants (such as phenolics, quaternary ammonium compound, and sodium hypochlorite) has been assessed in time-kill experiments.^{108,109} VRE was completely inactivated in 15 seconds by all disinfectants. MRSA was inactivated in 15-30 seconds with 10% bleach and Vesphene Ise (Steris), whereas Lysol products (Reckitt Benckiser) demonstrated inactivation in 30-60 seconds.¹¹⁰ The susceptibilities of antibiotic-resistant and antibiotic-susceptible bacteria to germicides are summarized in Table 4.

RELATIONSHIP BETWEEN ANTIBIOTIC RESISTANCE AND GERMICIDE RESISTANCE

Laboratory-Induced Reduced Susceptibility to Germicides

In the laboratory, it has been possible to develop mutants with reduced susceptibility to germicides that demonstrate decreased susceptibility or resistance to antibiotics¹¹¹⁻¹¹⁷ (Table 5). Moken et al.¹¹¹ 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 tetracycline, ampicillin, and chloramphenicol. The mechanism of resistance was likely enhanced efflux.¹¹⁸ Similarly, Price and coworkers¹¹⁹ reported that pine oil-resistant *S. aureus* demonstrated a reduced susceptibility to vancomycin (MIC, ≥ 1 $\mu\text{g}/\text{mL}$). Russell et al.¹¹² developed stable chlorhexidine resistance in some strains of *Pseudomonas stutzeri* by exposing the organisms to increasing concentrations of bisbiguanides. The chlorhexidine-resistant strains showed a variable reduced susceptibility to quaternary ammonium compounds, triclosan, polymyxin B, gentamicin, nalidixic acid, erythromycin, and ampicillin. Akimitsu and coworkers¹¹³ 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 Tomlinson¹¹⁵ selected for strains of *P. aeruginosa* with polymyxin resistance and showed that such strains developed decreased susceptibility to qua-

TABLE 5. Laboratory-Developed Pathogen Strains with Germicide-Linked Antimicrobial Resistance

Reference	Test organism	Agent	Germicide characteristic			Antimicrobial characteristic			
			MIC, µg/mL		Gene affected	Agent	MIC, µg/mL		Clinically significant difference in MIC ^a
			Initial	Final			Initial	Final	
Moken et al., ¹¹¹ 1997	<i>E. coli</i>	Pine oil	0.9 ^b	>4.1 ^b	<i>Mar</i>	Ampicillin	<1.2	8.5	No
						Tetracycline	1.8	>12.8	No
						Chloramphenicol	2.6	>35	Yes
Russell et al., ¹¹² 1998	<i>P. stutzeri</i>	Chlorhexidine	2.5 to 5	10 to 100	...	Triclosan	1	1 to 250	No
						Polymyxin B	<1	<1 to >500	No standard
						Gentamicin	<1 to 2.5	<1 to 100	Yes
						Erythromycin	25 to 50	5 to >200	No standard
						Ampicillin	10 to 100	100 to >500	No standard
Akimitsu et al., ¹¹³ 1999	MRSA	Benzalkonium chloride	5	10	...	Oxacillin	16	64 to 512	No
						Ampicillin	16	16 to 32	No
						Cefazolin	64	64 to 128	No
						Ofloxacin	8	16 to 32	No
						Tetracycline	125	32 to 128	No
						Kanamycin	256	256 to 512	No
						Chloramphenicol	4	4	No
						Tetracycline	0.5	40 to >256	Yes
						Ciprofloxacin	0.008	0.375 to 0.75	No
Chuanchuen et al., ¹¹⁷ 2001	<i>P. aeruginosa</i>	Triclosan	24	>128	<i>NfxB</i>	Trimethoprim	32	1,024 to >1,024	No standard
						Erythromycin	8	1,024 to >1,024	No standard
McMurry et al., ¹¹⁶ 1999	<i>M. smegmatis</i>	Triclosan	1.0	4.0 to 6.3	<i>InhA</i>	Isoniazid	1.0	8.5	No
Tattawasart et al., ¹¹⁴ 1999	<i>P. stutzeri</i>	Chlorhexidine diacetate	1 to 2.5	25 to 50	...	Triclosan	1 to 2.5	1 to 250	No
						Gentamicin	<1 to 2.5	<1 to >200	Yes
						Rifampin	2.5 to >200	2.5 to 10	No standard
						Erythromycin	25 to 100	5 to >200	No standard
						Ampicillin	10 to 100	100 to >500	No standard
						Tattawasart et al., ¹¹⁴ 1999	<i>P. aeruginosa</i>	Chlorhexidine diacetate	10
						Gentamicin	2.5	2.5	No
						Rifampin	25	25	No
						Erythromycin	100	100	No
						Ampicillin	>500	>500	No

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*.

^a 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 criteria⁶²).

^b 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 colleagues¹²⁰ 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.¹²¹ 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,¹²² other metals,¹²³ 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.⁸⁹ 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.¹²⁴⁻¹²⁷ Strains carrying *qac* genes may exhibit reduced susceptibility to aminoglycosides and/or tetracycline.¹²⁶ Coagulase-negative staphylococci frequently also contain *qac* genes.¹²⁸ Studies have established that the *qac* genes consist of 2 gene families, *qacCD* (now referred to as *smr*) and *qacAB*.

Triclosan is a synthetic, nonionic, broad-spectrum antibacterial and antifungal agent.^{129,130} Strains of *E. coli* with reduced susceptibility to triclosan have been developed in the laboratory as a result of mutations in the *FabI* gene.^{131,132} 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.^{133,134} 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.^{135,136} For example, enoyl-reductase targets have been found in *S. aureus*,¹³⁷ *S. pneumoniae*,¹³⁸ *P. aeruginosa*,¹³⁹ and *M. tuberculosis*.¹⁴⁰ Decreased susceptibility to triclosan has been reported in clinical specimens of *S. aureus*.^{141,142} However, strains with reduced susceptibility to triclosan were not more likely to demonstrate resistance to methicillin¹⁴¹ or other antibiotics.¹⁴² Investigators have also reported increased tolerance to triclosan due to mutations in efflux pumps of *E. coli*¹⁴³ and *P. aeruginosa*.^{117,144} In addition, increased tolerance to triclosan was produced with *Mycobacterium smegmatis*, and such strains demonstrated increased tolerance of isoniazid.¹¹⁶ 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 endemic¹⁴⁵ and epidemic MRSA¹⁴⁶ and outbreaks of *Clostridium difficile* infection.¹⁴⁷

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.¹⁴⁸ For example, in one survey, triclosan was found to be present in 76% of liquid soaps and 29% of bar soaps.¹⁴⁹ 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*.¹⁵⁰ 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 susceptibilities among staphylococci or gram-negative bacilli isolated from the hands of study subjects.^{151,152} 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."^{153(p13)}

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,¹⁵⁴ leading to approximately 88,000 deaths.¹⁵⁵ Disinfection^{57,58} and antiseptics⁵⁹ 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.⁵⁸ Critical items, comprising 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 valves¹⁵⁶ and intraocular lenses.^{157,158} 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,¹⁵⁹ and more than 30 outbreaks have been associated with gastrointestinal endoscopes.¹⁶⁰ 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,¹⁶¹ VRE,^{162,163} or *C. difficile*,^{164,165} has been documented. It is believed that all 3 organisms are often transmitted from patient to patient via the hands of healthcare workers. However, it has been impossible to distinguish contamination of the healthcare workers' hands due to direct patient contact from contamination due to contact with contaminated environmental surfaces. Evidence that disinfection of environmental surfaces in contact with the patient is important to prevent nosocomial transmission includes outbreaks traced to contaminated mobile radiograph equipment,¹⁶⁶ blood pressure cuffs,¹⁶⁷ and tubs used for bathing patients.^{168,169} These problems could be attributed to the failure to perform recommended disinfection of medical equipment. More recently, studies have identified proximity as a risk factor for nosocomial acquisition of *C. difficile*¹⁷⁰ and have demonstrated that enhanced environmental cleaning can reduce the incidence of *C. difficile*.¹⁷⁰⁻¹⁷³ The use of disinfectants on noncritical surfaces such as floors or walls is controversial. Arguments in favor of using disinfectants include the following: disinfectants are required for surfaces contaminated by blood or other potentially infectious material, disinfectants are more effective than detergents in reducing the microbial load on floors, detergents become contaminated and result in seeding the patient's environment with bacteria, and use of a single product for decontamination (ie, a disinfectant) of noncritical surfaces, such as floors and equipment, simplifies both training and compliance with appropriate practice.¹⁷⁴

The importance of handwashing with an antiseptic was first demonstrated by Semmelweis more than 140 years ago. Many studies have demonstrated that transient colonization of the hands of healthcare workers occurs with potentially pathogenic organisms, including MRSA, VRE, *C. difficile*, and gram-negative bacilli.⁵⁹ Similarly, many studies have demonstrated the efficacy of antiseptics for elimination of such transient flora and reduction of overall bacterial counts.^{59,175} Quasi-experimental studies have demonstrated that hand hygiene is associated with a reduction in nosocomial infections.¹⁷⁵ 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.¹⁷⁶ 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.¹⁷⁷

Despite the widespread use of disinfectants and antiseptics in hospitals, acquired resistance to current disinfectants has rarely been reported. For example, Klossner and colleagues¹⁷⁸ 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 colleagues¹⁷⁹ 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.¹⁸⁰⁻¹⁸⁴ 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%.¹⁸⁵ 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.¹⁸⁶ 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.¹⁸⁹ The impact of hand carriage and antiseptics 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, inhi-

bition 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 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 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 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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