Use of germicides in health care settings—is there a relationship between germicide use and antimicrobial resistance: A concise review

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A B S T R A C T

Despite the widespread use of disinfectants and antiseptics in hospitals, acquired resistance to current disinfectants has rarely been reported. Germicides, as with medications, should only be used when their benefit as demonstrated by scientific studies exceeds possible risks to human health or the environment.

BACKGROUND

The Centers for Disease Control and Prevention (CDC) stated, "Antibiotics are the foundation of modern medicine," and noted that antibiotics "have transformed health care around the world—making once deadly diseases treatable and saving millions of lives."[1] Not surprisingly, then, antibiotics are frequently administered to hospitalized patients. From 2006 to 2012, 55.1% of inpatients received at least 1 dose of antibiotics during their hospitalization, and the overall national days of therapy was 755 per 1000 patient days.[2] A prospective point prevalence study in 2007 of 14,414 patients in 1265 intensive care units from 75 countries reported that, on the day of study, 71% of all patients were receiving antibiotics.[3] Although antibiotics can be lifesaving, antibiotic use is associated with an increased risk of *Clostridioides difficile* and *Candida*, allergic reactions, drug interactions, adverse events (eg, renal failure), and development of antibiotic resistance.[1] Importantly, the CDC estimates that 30% to 50% of antibiotics prescribed in hospitals are unnecessary or inappropriate.[4] Further, the CDC has stated that, "There is no doubt that overprescribing and misprescribing are contributing to the growing challenges posed by *Clostridioides difficile* and antibiotic-resistant bacteria."[4] The World Health Organization has observed that, "Antibiotic resistance is one of the biggest threats to global health, food security, and development today."[5] The CDC has estimated that each year in the United States at least 2 million people get an antibiotic-resistant infection and at least 23,000 people die as a result.[6]

Antiseptics (eg, alcohol, chlorhexidine, iodine compounds) are widely used in health care for hand hygiene by health care personnel,[7,8] skin antisepsis for invasive procedures (eg, placement of a central venous catheter),[7,8] skin antisepsis of patients and surgical staff prior to surgery,[9] daily bathing of patients residing in an intensive care unit,[8] and oral care of intubated patients.[10] Low-level disinfectants (eg, sodium hypochlorite, quaternary ammonium compounds, improved hydrogen peroxide, quaternary ammonium compounds and alcohol) are recommended to be used in the United States for daily and terminal patient room cleaning and disinfection and for cleaning and disinfection of shared patient equipment.[11–13] High-level disinfectants and chemical sterilants (eg, glutaraldehyde, *ortho*-phthalaldehyde) are used to perform high-level disinfection on semicritical items (eg, gastrointestinal endoscopes, vaginal specula, laryngoscopes) or chemical sterilization of heat-sensitive critical items.[11–13]

Given the growing threat of antibiotic resistance, the issue of whether there is cross-resistance in bacteria between antibiotics and germicides used in health care has been repeatedly raised in recent decades. The twofold issues are (1) whether antibiotic-resistant bacteria is more likely to exhibit resistance to one or more germicides than a similar but non-antibiotic resistant strain, and (2) whether bacteria that demonstrate increased tolerance or reduced susceptibility to germicides are more likely to exhibit antibiotic resistance. The issues of cross-resistance between antibiotics and germicides have been reviewed.[14–25]

TERMINOLOGY

The importance of using the proper terminology when discussing the relationship between antibiotic and germicide resistance has

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Table 1
Similarities and differences between antibiotic and germicide resistance

Similarities
Intrinsic resistance (eg, spores are resistant to alcohols) and extrinsic resistance (eg, efflux pumps for heavy metals) are well described.
Acquired mechanisms of resistance are similar (eg, impermeability, efflux pumps).
Biofilms impair inactivation/killing.
Inactivation is dependent on the concentration and duration of contact with the antibiotic or germicide.
Differences
Most antibiotics inhibit a specific target in a biosynthetic process.
Most biocides have multiple concentration-dependent targets, with subtle effects occurring at low concentrations and more damaging ones at higher concentrations.

been emphasized in several reviews.[16–18,24] Biocidal agents (also termed germicides), including antiseptics (germicides used on the skin) and disinfectants (germicides used on surfaces or patient instruments and equipment), inactivate microorganisms. Disinfectants with high-level effectiveness inactivate all microorganisms, with the exception of high numbers of 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 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, temperature) and the actual clinical efficacy of the therapy (eg, host defenses, site of infection, 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, beta-lactamases), and the clinical efficacy of agents to inhibit these strains has not been reliably demonstrated in treatment studies. In contrast to its precise use in reference to antibiotic therapy, the term "resistant" has been used loosely when referring to the 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. The more accurate terms are "reduced susceptibility" or "increased tolerance."

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 concentrations in more concentrated products).

MECHANISMS OF BACTERIAL RESISTANCE TO ANTIBIOTICS AND GERMICIDES

As noted above, antibiotic resistance in several common human pathogens is a worldwide problem. Antimicrobial resistance may be intrinsic (an inherent property of the specific bacterial species) or acquired. Mechanisms of intrinsic resistance include cell impermeability and efflux.[16,17] Common mechanisms of acquired resistance include the following: target site alteration, altered cell permeability, enzymatic modification or destruction, bypass of sensitive steps, or efflux pumps.[14,16,17] The mechanisms of germicide resistance are similar to those responsible for antibiotic resistance, but there are some differences (Table 1).

Table 2
Selected studies comparing germicide susceptibility in antibiotic resistant and susceptible strains

Author (year)	Bacteria studied	Germicides evaluated	Results
Al-Masaudi et al (1988)[26]	*Staphylococcus aureus* (MSSA, MRSA)	Phenolics, chlorhexidine	All strains were inactivated at the recommended germicide concentrations.
Anderson et al (1997)[27]	*Enterococcus* (VSE, VRE)	QAC, phenolic, iodophor	All strains were inactivated at the recommended germicide concentrations.
Rutala et al (1997)[28]	*S aureus* (MSSA, MRSA), *S epidermidis*, *Enterococcus*, Escherichia *coli*, *Pseudomonas aeruginosa*, *Salmonella choleraesuis*	Phenolic, QAC	In 20 comparative trials, only once did the antibiotic resistant strain exhibit reduced susceptibility to a germicide.
Sakagami and Kajimura (2002)[29]	*Enterococcus* (VSE, VRE)	Alcohol, chlorhexidine, glutaraldehyde, formalin	All strains were inactivated at the recommended germicide concentrations.
Rutala et al (2006)[30]	*S aureus* (MSSA, MRSA), *Enterococcus* (VSE, VRE)	Alcohol, chlorine, benzyl ammonium chloride, phenolic	All strains were inactivated at the recommended germicide concentrations.
Wisplinghoff et al (2007)[31]	Acinetobacter *baumannii*	Alcohol, chlorhexidine, iodine, triclosan	All strains were inactivated at the recommended germicide concentrations.
Koo et al (2012)[32]	*Klebsiella* (NDM-1)	Alcohol, chlorine dioxide	Routine disinfection was successful in curtailing this outbreak.
Robustillo et al (2012)[33]	*Klebsiella pneumoniae* (KPC)	Alcohol, chlorhexidine, benzalkonium chloride	Routine disinfection was successful in curtailing this outbreak.
Campos et al (2012)[34]	MRSA	Sodium hypochlorite, chlorhexidine, QAC	All strains were inactivated at the recommended germicide concentrations.

KPC indicates Klebsiella pneumoniae carbapenemase; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-susceptible *Staphylococcus aureus*; *NDM-1*, New Delhi metallo-β-lactamase; *QAC*, quaternary ammonium compound; *VRE*, vancomycin-resistant *Enterococcus*; *VSE*, vancomycin-susceptible *Enterococcus*.

Table 3
Summary of the relationship between germicide use and antibiotic resistance

Question	Answer
Does the use of disinfectants or antiseptics result in disinfectant and/or antiseptic resistance to the recommended concentrations of the antiseptics or disinfectants?	No
Do antibiotic-resistant bacteria exhibit resistance to the recommended concentrations of antiseptics or disinfectants?	No
Does the use of currently recommended hospital disinfectants and/or antiseptics precipitate antibiotic resistance?	No
Does the recommended use of antiseptics and disinfectants in hospitals decrease the burden of health care–associated infections?	Yes
Conclusion: Regarding the continued use of antiseptics and disinfectants as currently recommended, the benefits overwhelming exceed the risks.	

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 antibiotics. Reduced susceptibility was most commonly shown to chlorhexidine, benzalkonium chloride, and triclosan. Importantly, the latter 2 agents are no longer used in health care facilities.

INACTIVATION OF ANTIBIOTIC-RESISTANT BACTERIA BY DISINFECTANTS

Multiple investigations of laboratory-induced cross-resistance have frequently tested antibiotics that are of limited or no clinical relevance (Table 1).[26–34] Although some investigators described reduced susceptibility to some germicides, resistance to recommended use concentrations of the germicides was not reported. Disinfectant classes tested included alcohols, aldehydes, iodine compounds, cation surfactant and amphoteric compounds, and biguanide-containing agents. Rarely, clinical or environmental bacterial isolates, some associated with outbreaks, have demonstrated survival at high or in-use concentrations of antiseptics or low-level disinfectants.[21] To date, widespread dissemination of a bacterial strain resistant to the in-use concentration of commonly used hospital antiseptics or disinfectants has not been reported. In addition, the susceptibility of antibiotic-resistant pathogens to surface disinfectants used at the appropriate dilution has been investigated. When germicides were diluted to their recommended use dilution (or even below), antibiotic-resistant pathogens did not demonstrate reduced susceptibility to germicides (Table 2). Table 3 summarizes the relationship between germicide use and antibiotic resistance.

RELEVANCE OF *QAC* GENES IN STAPHYLOCOCCI

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 methicillin-resistant *Staphylococcus aureus* strains. Tolerance is mediated by the *QAC* family of genes, which 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 *QACAB*.

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