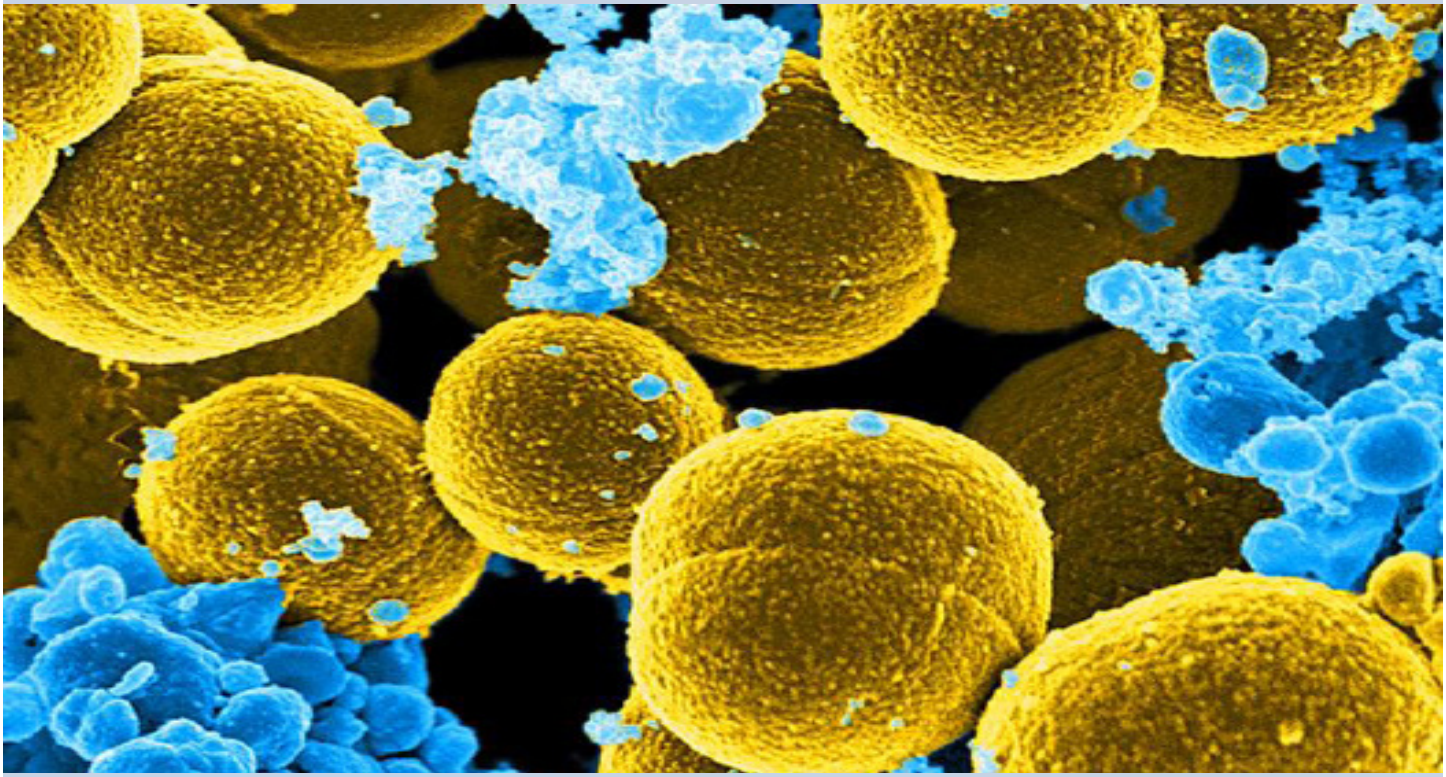
Antimicrobials in Hospital Furnishings: Do They Help Reduce Healthcare-Associated Infections?



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Health Care Without Harm

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Executive Summary

Manufacturers of healthcare furnishings[i] have been developing new products with antimicrobial properties to protect materials from degradation, for aesthetic reasons, and to reduce microbial burdens on product surfaces, anticipating that this may help reduce the risk of healthcare-associated infections (HAIs). Industry experts predict hospitals will continue to increase purchases of products containing antimicrobials. Antimicrobial use in other consumer products, including items for food production and storage, personal care, clothing, household goods, and building materials, is also increasing. These uses collectively add to the potential for general population and environmental exposures. Unfortunately, data on the safety and efficacy of this growing practice are scarce, and potential unintended consequences have not been fully explored.

Healthcare-associated infections have always been a formidable challenge in hospitals and are major causes of morbidity and mortality today. Healthcare-associated infections can prolong the length of hospital stays, result in readmission after discharge, and increase costs to individuals, families, and communities. Moreover, under provisions of the Affordable Care Act, preventable readmissions can result in a financial penalty in reimbursement for all Medicare patients at that hospital. This has driven an interest in developing new strategies to reduce HAIs.

Although some antimicrobials clearly reduce the microbial load on textiles and other environmental surfaces in laboratory settings, they have rarely been evaluated in well-designed clinical studies for their effectiveness in contributing to HAI reduction. While antimicrobials in hospital furnishings may ultimately prove to be efficacious, currently the benefits, risks, tradeoffs, and costs associated with their use are largely unknown.

Beyond their potential impact on HAIs, life cycle safety concerns associated with the manufacture, use, and disposal of antimicrobials need careful consideration. Releases into the indoor and outdoor environments can result in unwanted exposures to humans, wildlife, and ecosystems with adverse and sometimes unanticipated consequences. Historically, failure to examine life cycle benefits and risks of other chemical agents have resulted in nearly ubiquitous exposures with adverse human health and environmental effects discovered years later, after irreparable damage is done.

The growing use of products containing antimicrobials can also further increase the risk of antibiotic resistance, engender a false sense of security with reduced attention to cleaning and disinfection, and increase costs of products and materials.

Evaluation of the benefits at the point of use, life cycle risks, tradeoffs, and financial implications of adding antimicrobials to products in hospitals will help product designers, purchasers, infection preventionists, and environmental services personnel make informed decisions. Until then, design and purchasing decisions will be based mostly on unverified assumptions rather than objective data.

Healthcare administrators and staff, clinicians, and product manufacturers each have opportunities to help generate the data necessary to justify the growing use of antimicrobial agents in hospital furnishings. Demonstrated efficacy of added antimicrobials with reduction in HAIs as part of a comprehensive infection control program and life cycle safety evaluations are essential. Until then, we make the following recommendations.

Recommendations

The benefits, risks, tradeoffs, and cost implications of adding antimicrobials to furnishings are active areas of research. These recommendations are based on a current evaluation of the state of the science with the expectation that more objective data will aid in making informed design and purchasing decisions.

For health care

These recommendations are offered as a complement to comprehensive integrated infection surveillance and control programs.

[i] Here the term "furnishings" includes surfaces (tables, desks, countertops, etc.), built-in and modular casework, seating, beds, bedding, cubicle curtains, window coverings, panels and partitions, storage and shelving.

- Do not specify antimicrobials in furnishings unless they have undergone U.S. Environmental Protection Agency (EPA) evaluation and registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and have been shown to help reduce HAIs in a clinical setting as part of an integrated infection control program.
- Ask suppliers to disclose any antimicrobials added to materials and products, even if they are used for the purpose of material preservation, the control of odor, or some other aesthetic reason.
- Take the lead or collaborate in the design and execution of a research agenda intended to address data gaps related to efficacy and risks associated with adding antimicrobials to furnishings.
- Examine antibiotic stewardship programs in your institution for opportunities to reduce the risk of generating antimicrobial resistance.
- Examine antibiotic stewardship programs in your community for opportunities to reduce the risk of generating antimicrobial resistance, including in animal agriculture. Help make the case that antibiotic stewardship to address the growing problem of antimicrobial resistance is a community-wide responsibility.

For furnishings manufacturers

- Do not make antimicrobials the standard option for any products, with the exception of antimicrobials that are used solely for product protection. Antimicrobials should be a "must select" option in order to make the decision clear, as well as to track the demand for products containing antimicrobials.
- Use only antimicrobials that have undergone EPA evaluation and registration under FIFRA and have been shown to reduce the risk of HAIs in a clinical setting unless using them is in the context of a research program to examine their efficacy.
- Take the lead or collaborate in the design or execution of a research agenda intended to fill data gaps related to efficacy and risks associated with adding antimicrobials to furnishings.
- Require full toxicity testing, studies of potential leaching, and evaluations of potential human or environmental exposure to any antimicrobials used in products.
- Align sales and marketing claims with EPA FIFRA labeling requirements.
- Investigate and make publicly available information about the presence of all antimicrobials in products, including antimicrobials that are exempt from FIFRA registration because of the Treated Articles Exemption.

For manufacturers of antimicrobials

- Conduct full toxicity testing, including environmental toxicity, fate, and transport, as well as life cycle assessment of any antimicrobials, including antimicrobials used for purposes of preserving the product, and make results publicly available.
- Collaborate to develop clinically-relevant testing methods to determine efficacy in the clinical setting.
- Align sales and marketing claims with EPA FIFRA labeling requirements.
- Commit to transparency in toxicity and efficacy testing for all antimicrobials.

For the research community

- Prioritize research to determine efficacy, risks throughout the life cycle, tradeoffs, and cost implications of the use of antimicrobials in furnishings in clinical settings.
- Research hazard profiles and potential human and environmental exposures to antimicrobials used for purposes of preserving the product.
- Research whether the addition of antimicrobials in products changes the microbial ecology (microbiome) of a building or spaces within a building and whether those changes have clinical or public health significance.

> **The bringing together within a confined area of many sick persons is perilous. The risks of contamination of the air and of impregnation of the materials of the building with morbid substances are so greatly increased, that the greatest care is necessary that hospitals should not become pesthouses, and do more harm than good. There is indeed a continual sacrifice of life from diseases caught in or aggravated by hospitals. The risk is least in the best ventilated hospitals. A great supply of air by immediately diluting and rapidly carrying away the morbid substances evolved in such quantities from the bodies and excretions of the sick reduces the risk to its minimum.**

Simpson JY. Presidential address; on public health. Trans Natn Ass Promotion Social Sci 1867; 107-123. (cited in Selwyn, 1991)

Introduction

Healthcare-associated infections (HAIs) have been part of health care delivery since antiquity and are major causes of morbidity and mortality today. Attention to building design, operations, hand washing, cleaning, disinfection, and surveillance are proven methods for preventing and controlling HAIs. Yet, strict adherence to guidelines is challenging, and many hospital administrators and infection preventionists ask, "What more can we do? What can we add?"

In response, a number of manufacturers are producing furnishings[i] with embedded antimicrobial agents. Health care systems consider purchasing these furnishings to supplement infection control programs, hoping they will help reduce the risk of HAIs. This paper considers whether that hope is justified.

Beginning with a brief historical summary, it traces the emerging frame of HAIs as a systems problem in need of systems-based solutions. Even though completely eliminating HAIs is unlikely to be a realistic goal, clearly there is room for improvement, and emerging technologies may demonstrate added value. Among the newer interventions, does the addition of antimicrobial agents to an assortment of products and materials in the health care setting help reduce the incidence of HAIs? What's the evidence? Are there associated risks, tradeoffs, and cost implications that should inform decision-making?

[i] Here the term "furnishings" includes surfaces (tables, desks, countertops, etc.), built-in and modular casework, seating, beds, bedding, cubicle curtains, window coverings, panels and partitions, storage and shelving.

The Problem: Healthcare-Associated Infections

Based on surveys of 183 acute care hospitals, the Centers for Disease Control and Prevention (CDC) estimates that there were about 722,000 HAIs in the United States in 2011.[1, 2] Approximately 75,000 hospital patients with HAIs died while hospitalized. Infants up to one year of age, the elderly, and long-term patients were at highest risk, but HAIs were seen in all age groups. More than half of HAIs occurred outside of an intensive care unit (ICU), but the risk of acquiring a HAI in an ICU was about 30 percent higher than in other areas.

The survey found the major HAIs were pneumonia (22 percent), surgical site infections (22 percent), gastrointestinal (17 percent), central line and other device-associated blood stream infections (10 percent), and urinary tract infections (13 percent). Just 25 percent of HAIs were related to use of devices like catheters and ventilators.

A growing proportion of these infections are caused by antibiotic-resistant pathogens, also referred to as multidrug-resistant organisms (MDROs), such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* (*C diff*), vancomycin resistant enterococci (VRE), and carbapenem-resistant enterobacteriaceae (CRE). Viruses can also cause HAIs, including HIV, hepatitis B, noroviruses, coronaviruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and Avian influenza in humans. Occasionally, fungi, parasites, and prions are implicated.

Acquisition and transmission of HAIs[3]

Acquisition and transmission of infectious agents within a health care setting requires three things: a source of an infectious agent, a susceptible host with a route of exposure receptive to the agent, and a mode of transmission. All three are needed to complete the chain of transmission.

Sources of infectious agents

Healthcare-associated infectious agents come mainly from humans, but contaminated environmental objects and substances—e.g., air, food, water, table tops, and other surfaces—can be involved in transmission from one person to another. Patients, health care personnel, household members, and other visitors carry responsible microbes. People may have active infections with or without symptoms or be transiently or chronically colonized with pathogens, particularly in the respiratory and gastrointestinal tracts. The endogenous flora of patients' skin, lungs, nasal passages, and gastrointestinal tract can all be a source.

Host susceptibility

Some people exposed to pathogenic infectious agents never develop symptomatic disease while others become severely ill and even die. Some people are prone to becoming transiently or permanently colonized—i.e., the organism is present but does not cause a clinical infectious illness (for example, with MRSA)—but remain asymptomatic. Others progress from colonization to symptomatic disease following exposure or after a period of asymptomatic colonization. Given the relatively short, episodic length of stay for most patients in acute-care hospitals, exposure to pathogens can occur in the hospital with symptoms of active infection appearing days or weeks after discharge.

The status of a person's immune system, interactions among a patient's own normal microbial flora and those newly encountered during hospitalization, as well as virulence factors intrinsic to the infectious agent are important predictors of outcome after an exposure. Age and underlying disease status, such as diabetes, malignancy, or HIV infection, can influence susceptibility to infectious diseases. Medications such as antibiotics, steroids, anti-organ transplant-rejection drugs, immunosuppressants, and cancer chemotherapeutics can also increase susceptibility through a variety of mechanisms. In these settings, microorganisms that would not ordinarily be particularly pathogenic can become more virulent.

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Surgical procedures and radiation therapy impair defenses of the skin and other involved organ systems and provide portals of entry for microorganisms. Indwelling devices such as urinary catheters, endotracheal tubes, vascular catheters, and synthetic implants allow potential pathogens to bypass local defenses and provide surfaces for the development of biofilms that may reduce the effectiveness of antibiotics.

Modes of transmission

Contact transmission

Microorganisms can be transferred from an infected person to someone else directly or via an intermediate person or object. For example, a health care worker may develop an infection after direct contact with infected blood or other body fluid from a patient. Alternatively, a health care worker may transfer a hand-borne infectious agent to a patient during patient care. Indirect transmission involves the transfer of an infectious agent via a contaminated intermediate object—e.g., a medical device, chair, table, bed railing, pen, paper, contaminated toy, or clothing.

Droplet transmission

Respiratory droplets containing infectious agents are produced when an infected person coughs, sneezes, or talks, as well as during various procedures such as suctioning, endotracheal intubation, cough induction for respiratory therapy, or cardiopulmonary resuscitation. Generally these droplets are transported over relatively short distances (e.g., 3-6 feet) and may be deposited on nearby surfaces or directly contact a nearby person. The effectiveness of droplet transmission also depends on the viability of agents within the droplets.[4]

Airborne transmission

Airborne transmission occurs by inhalation of airborne aerosols or small particles containing infectious agents that remain infective over time and distance—e.g., spores of some fungi and *Mycobacterium tuberculosis*. Air currents carrying these agents may be dispersed over fairly long distances and inhaled by people who have not been in contact or even in the same room with the infected person. The extent to which MERS CoV and some other viruses can be transmitted in this way is uncertain but likely over a distance of 3-6 feet, although it may be longer if the patient with infection is undergoing an aerosol-generating procedure like endotracheal intubation.

Fecal-oral transmission

Fecal-oral transmission involves microorganisms that infect the gastrointestinal system. Improper hygiene and sanitation practices can result in food or water contamination or deposition of pathogens on surfaces touched by other patients or health care workers.

Vector-borne transmission

Examples of vectors are flies, mites, fleas, ticks, mosquitoes, or rodents that harbor infectious agents that can be responsible for serious diseases. Many years ago typhus, for example, a louse-borne rickettsial disease, was a serious HAI in health care facilities. Fumigation and disinfection or burning of infested clothing were used in response.[5]

Efforts to control healthcare-associated infections: A brief history

The history of heathcare-associated infections is a long one. Sydney Selwyn, physician, microbiologist, and medical historian, opened the 1990 Second International Conference of the Hospital Infection Society with an interpretation of that history reaching back over 2500 years.[6] After briefly discussing institutions that preceded modern hospitals, Selwyn jumped to 500 BCE when "organized hospitals for the care of the sick existed throughout the civilized world...notably in India, Palestine, and Greece. The hygienic conditions which prevailed were mainly based on religious concepts of ritual purity and seem to have been greatly superior to those that were tolerated less than 100 years ago in the hospitals of Christian Europe."

Attention to cleanliness, bathing facilities, and one or two person rooms open to the air surrounding a central courtyard are featured in ruins and reconstructions of ancient hospitals. Selwyn cites the earliest documented advice on hospital construction and hygiene from the Charaka-Samhita, a Sanskrit textbook of medicine, likely written in the fourth century BCE:

"In the first place a mansion must be constructed under the supervision of an engineer well-conversant with the science of building mansions and houses. It shall be spacious and roomy . . . One portion at least should be open to the currents of wind. It should not be exposed to smoke, or dust, or injurious sound or touch or taste or form or scent. After this should be secured a body of attendants of good behavior, distinguished for purity and cleanliness of habits."[7]

Religious beliefs heavily influenced construction and activities in hospitals during the medieval and Renaissance periods in Europe and Islamic countries. Many of them looked like churches or mosques. [8, 9, 10]

Selwyn found that the early Christian church was unique among religions in being opposed to washing and caring for the body.[11] With Christianity, body and soul became more connected and illnesses were more easily tied to sin. Early European hospitals cared for people who were poor, homeless, and generally destitute, but care for their souls was generally thought to be more important than care of their bodies. Overcrowding, bed sharing, and poor hygiene were common. High-level endemic communicable disease was a norm.

Scientific study of healthcare-associated infections began during the first half of the 18th century, with many of the most important initial contributions coming from Scotland.[12] Physician Sir John Pringle strongly believed that overcrowding and poor ventilation increased the risk of hospital-acquired infection and urged changes in military hospitals. The germ theory of infectious disease was not yet even proposed, but Pringle and others who followed made epidemiologic observations that confirmed what others had apparently observed many centuries before. Pringle wrote:

"As to the disposition of hospitals, with regard to preserving the purity of the air, the best rule is, to admit so few patients into each ward, that a person unacquainted with the danger of bad air, might imagine there was room to take in double or triple the number. It will also be found a good expedient, when the cielings (sic) are low, to remove some part of them, and to open the garret story (sic) to the tiles. It is surprising in how few days the air will be corrupted in close and crowded wards; and, what makes it hard to remedy the evil, is the difficulty of convincing either the nurses or the sick themselves, of the necessity of opening the doors or windows at any time for air. I have generally found those wards the most healthful, when by broken windows, and other wants of repair, the air could not be excluded."[13]

In the mid-19th century Florence Nightingale also promoted fresh air along with general cleanliness and hygiene with extraordinarily beneficial responses. Her leadership in improving conditions in military hospitals, including spatial separation of patients and introduction of sunlight and natural ventilation led to dramatic reductions in HAIs among soldiers receiving care.[14] She also introduced and promoted statistical analysis of hospital data in order to demonstrate the role of hygiene in reducing mortality from infectious disease.[15] But she never subscribed to the germ theory of disease, believing that HAIs were a more general atmospheric problem.

Large hospital outbreaks of puerperal fever in the 18th century, undoubtedly due to *Streptococcus pyogenes,* sparked investigations showing that the disease was most commonly transmitted by a clinician from one patient to another and not due to some foul quality of the atmosphere. Ignaz Semmelweis famously demonstrated a tenfold reduction in puerperal fever after clinicians washed their hands in a solution of chlorinated lime between patients and recommended widespread adoption of that practice.[16] But he was ridiculed for having no scientific basis to explain this, became depressed, was admitted to an asylum and soon died. Oliver Wendell Holmes' 1843 paper "The Contagiousness of Puerperal Fever" supported Semmelweis' conclusions, but it was not until the work of Louis Pasteur and Robert Koch, Koch's postulates, and the emergence of the germ theory of infectious disease that disagreements were resolved.[17] Only a few years after Semmelweis died, Joseph Lister applied the theory with sanitary practices in hospitals and aseptic surgical techniques using carbolic acid as an antiseptic.[18]

Improved hygiene, use of antiseptics, and reduced virulence of the organism combined to decrease the incidence of puerperal fever. The development of sulfonamides and penicillin in the first half of the 20th century transformed treatment of the disease.

Healthcare-associated infections with *Staphylococcus aureus* became increasingly prominent in the early 20th century, and laboratory evidence showed that increased virulence as well as antibiotic resistance contributed. The development of methicillin helped enormously in treatment, but methicillin-resistant strains emerged, and infections with MRSA remain a challenge today not only in hospitals but increasingly in communities.[19]

As health care and community circumstances continued to change in the 1950s and 1960s, HAIs due to gram-negative bacteria, including Escherichia, Klebsiella, Proteus, and Pseudomonas posed new challenges.[20] These organisms were often both antibiotic- and antiseptic-resistant and could survive in adverse environmental conditions. They emerged in the context of increasing numbers of susceptible, immunocompromised patients, antibiotic use, and development of more invasive diagnostic and therapeutic techniques that provided portals of entry.

In 1941, the British Medical Research Council recommended that "full-time special officers should be appointed to supervise the control of infection" using various means.[21] Infection control committees followed. The first infection control nurse was appointed in Exeter in 1959, and similar positions were established in US hospitals during the 1970s. Then, as now, infection control nurses and committees must navigate through delicate and sometimes uncomfortable relationships among administrators, clinicians, environmental services staff, purchasers, microbiologists, building designers, and architects. Interactions among them and their daily practices create system conditions that foster or reduce the risk of HAIs.

The effectiveness of HAI surveillance and control programs was first assessed in the United States by the CDC in the 1970-1976 Study on the Efficacy of Nosocomial Infection Control (SENIC Project).[22] Surveillance activities are designed to look for and quickly identify HAIs so that they can be treated and their spread controlled. In this study, a representative sample of United States general hospitals was evaluated. The presence of a well-trained infection control physician or microbiologist involved in an infection control program and at least one infection control nurse per 250 beds was associated with a 32 percent lower rate of four infections—central venous catheter-associated bloodstream infections, ventilator-associated pneumonias, catheter-related urinary tract infections, and surgical site infections.

The measures that seemed to be most effective differed for different sites of infection. A program with both surveillance and control components that reported surgical wound infection rates to hospital surgeons helped in the design of efforts to prevent these infections from occurring in the first place. An intensive surveillance program with minimal control activities was most effective for preventing urinary tract infections and postoperative pneumonias. Intensive control activities with moderate levels of surveillance helped to prevent healthcare-associated blood-borne infections. These differences showed that a program aimed at preventing infections at one site might not be very effective at preventing them at other sites. But preventing infections at all sites seemed to require the most intensive program of surveillance and control activities.

Since the SENIC study, the health care system has become more complex and the mix of patient populations and their illnesses have changed. Increasing numbers of medical procedures and devices are used in health care settings. Risks of HAIs vary in ICUs, burn units, medical-surgical units, and pediatrics, as well as long-term and ambulatory care facilities. In hospitals and communities new pathogens have emerged, some of which are increasingly resistant to treatment after an infection is established. Integrated administrative measures, adherence to guidelines, education, and surveillance in various combinations are necessary to prevent and control HAIs.

The long history of HAIs and evidence that discrete interventions are not adequate to eliminate them has led to the understanding that meeting this challenge necessitates a complex systems approach requiring structural and adaptive systems of surveillance and control.

Healthcare-associated infections: A systems problem needing system-level responses

Systems problems feature dynamic interactions among multiple, multi-level variables with positive and negative feedback loops creating conditions out of which an outcome of interest emerges. The effect of a single input into a complex system is difficult to predict without studying its impact on the functioning of the system as a whole. Understanding infectious disease transmission generally as a systems problem has greatly aided surveillance and control.[23]

Based on the following generally agreed upon observations, it's quite clear that the origins, prevention, surveillance, and control of HAIs are complex systems problems requiring systems-based responses:

- Healthcare-associated infections result from interactions among: a) infectious agents, b) successful routes of exposure, and c) susceptible hosts.
- Factors inside and outside health care facilities contribute to the convergence of events leading to HAIs.
- The presence of infectious agents in a hospital and their virulence depend on:
  - The microbial ecology of current and past patients, staff, visitors, and the surrounding community;
  - Building design, operation, and maintenance.
- Historic and recent antibiotic use and prescribing practices in the hospital and community, including in animal agriculture, help to select for multi-drug resistant organisms (MDROs), which can then proliferate, become established, and pose more challenging risks of infection.[24, 25]
- Opportunities for exposure to infectious agents depend on:
  - Building ecology, including design, operation, and maintenance (e.g., ventilation, cleaning and disinfection practices);
  - The mix of medical diagnostic and therapeutic procedures and use of medical devices.
- Host susceptibility depends on the age and health status of individuals.
- Successful prevention, surveillance, and control of HAIs require coordinated efforts of people from various departments within the health care setting and from the surrounding community as well—e.g., clinicians, environmental services personnel, administrators, farmers and ranchers who use antibiotics, long-term care facilities, and public health departments.
- Prevention and control of HAIs have both technical and adaptive components. Technical components are key items in the toolkit or bundle of interventions—devices and products. Adaptive components involve attitudes, beliefs, perceptions, and behaviors of health care workers with respect to implementation of prevention control measures.[26]

The Institute for Healthcare Improvement's (IHI) monograph Using Care Bundles to Improve Health Care Quality makes a strong case for combining interventions into "bundles" in order to address systems problems like HAIs.[27] A bundle is "a small set of evidence-based interventions for a defined patient segment/population and care setting that, when implemented together, will result in significantly better outcomes than when implemented individually."

The first two bundles developed by IHI, in collaboration with 13 hospitals and the Voluntary Hospital Association, addressed delivery of care in intensive care units and focused on care of ventilator patients and patients in whom a central line was placed. Each bundle consisted of five evidence-based elements and the idea was to develop communication, coordination, and practices that would ensure that all elements of the bundle were consistently applied. Fairly good compliance with all elements of the bundles were achieved over a period of time and patient outcomes substantially improved, with decreased pneumonia and other adverse outcomes associated with ventilator use and decreased central line-associated infections.[28, 29] Since then, additional bundles for perinatal care and sepsis management have resulted in improved patient outcomes and cost savings.

It is important to note that these bundles were designed with evidence-based elements around which there was little controversy. That was intentional since the objective was to study the value of combining individual interventions already known to have value and not start debates about the utility of each. But questions about the quality of evidence underlying a proposed intervention remain important and deserve a closer look.

Grading evidence

In 1988, the Agency for Healthcare Research and Quality (AHRQ) designated three levels of evidence of scientific data for decision-making: high or 'A' – evidence based on randomized controlled clinical trials (RCTs) or meta-analyses; medium or 'B' – evidence based on well-designed, non-randomized clinical trials or data from cohorts or case-control studies; and low or 'C'.

In 2000, a working group came together to address the need for further development of guidelines for assessing the quality of evidence used to make decisions that ultimately lead to recommendations for clinical care. Their criteria and methods, known as Grading of Recommendations Assessment, Development and Evaluation (GRADE), are fairly widely used. [30, 31] The GRADE approach also privileges RCTs but acknowledges that they are not always feasible when evaluating potential interventions. Moreover, among RCTs their quality can vary significantly and well-designed non-randomized or observational studies can provide evidence of sufficient quality to justify action.

But some interventions intended to address a given problem can also have adverse consequences that complicate decision-making—e.g., unwanted side-effects of pharmaceuticals or the emergence of MDROs from overuse of antibiotics and the collateral impact of increasing incidence of *C. difficile* infections—requiring consideration of tradeoffs.

The GRADE working group recommends the following definitions when dealing with these trade-offs:

- Net benefits = the intervention clearly does more good than harm.
- Trade-offs = there are important trade-offs between the benefits and harm.
- Uncertain trade-offs = it is not clear whether the intervention does more good than harm.
- No net benefits = the intervention clearly does not do more good than harm.

The working group also concluded that people making a recommendation about a proposed intervention should consider four main factors:

1. The trade-offs, taking into account the estimated size of the effect for the main outcomes, the confidence limits around those estimates, and the relative value placed on each outcome
2. The quality of the evidence
3. Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects
4. Uncertainty about baseline risk for the population of interest. If there is uncertainty about translating the evidence into practice in a specific setting, or uncertainty about baseline risk, this may lower confidence in a recommendation

GRADE classification scheme for grading the quality of evidence

These are recommendations for grading evidence and guiding recommendations for clinical care. They can also aid in assessing interventions intended to reduce the risk of HAIs.

1. High: Highly confident that the true effect lies close to that of the estimated size and direction of the effect. Evidence is rated as high quality when there is a wide range of studies with no major limitations, there is little variation between studies, and the summary estimate has a narrow confidence interval.
2. Moderate: The true effect is likely to be close to the estimated size and direction of the effect, but there is a possibility that it is substantially different. Evidence is rated as moderate quality when there are only a few studies and some have limitations but not major flaws, there is some variation between studies, or the confidence interval of the summary estimate is wide.
3. Low: The true effect may be substantially different from the estimated size and direction of the effect. Evidence is rated as low quality when supporting studies have major flaws, there is important variation between studies, the confidence interval of the summary estimate is very wide, or there are no rigorous studies, only expert consensus.

Virtually all healthcare organizations attempting to prevent, identify through surveillance, and control HAIs recognize the need for multidimensional, coordinated efforts.[32] Current CDC guidelines for preventing transmission of infectious agents in health care settings[33] are briefly summarized here. Readers making administrative- or treatment-related decisions are encouraged to refer to the entire document.

- Hand hygiene remains the single most important practice to reduce the incidence of HAIs.
- Personal protective equipment—like gloves, gowns, and masks—and safe work practices help to protect the health care worker.
- Decisions about patient placement in single, double, or multi-bed wards can influence the risk of HAIs. This is particularly important if a patient is infected with an agent that can be transmitted by aerosol or droplets.
- Cleaning and disinfecting noncritical surfaces in patient-care areas are among standard precautions. Cleaning and disinfection of all patient-care areas is important for frequently touched surfaces, especially those closest to the patient, that are most likely to be contaminated (e.g., bedrails, bedside tables, commodes, toilets, doorknobs, sinks, call buttons).
- The frequency or intensity of cleaning may need to change based on the patient's level of hygiene, the degree of environmental contamination, and for certain infectious agents from the intestinal tract.
- In all healthcare settings, administrative, staffing, and scheduling activities should prioritize the proper cleaning and disinfection of surfaces that could be implicated in transmission.
- During a suspected or proven outbreak where an environmental reservoir is suspected, routine cleaning procedures should be reviewed, and the need for additional trained cleaning staff should be assessed
- Adherence should be monitored and reinforced to assure that consistent and correct cleaning is performed.

The CDC's Guideline for Disinfection and Sterilization in Heathcare Facilities, 2008 [34] presents evidence-based recommendations on the preferred methods for cleaning, disinfection, and sterilization of medical devices and for cleaning and disinfecting the health care environment.

Methods for evaluating the thoroughness of cleaning and disinfection are summarized in Appendix A.

Sterilization, disinfection and cleaning: How do they differ and how are they evaluated?

Sterilization, disinfection, and cleaning have distinct and different meanings.[35] The surfaces that require cleaning, disinfection, or sterilization are classified according to their potential to transmit an infection at the time of use.

- Sterilization is intended to eliminate all forms of microbial life.
- Disinfection results in a lower level of antimicrobial activity that inactivates virtually all metabolically active organisms but not necessarily all inactive forms like spores. High-level, intermediate-level, and low-level disinfection will eliminate varying levels of active and inactive microorganisms and are accomplished with various disinfectants.
- Cleaning refers to the removal of soil and organic contamination from a device or environmental surface using the physical action of scrubbing, the chemical action of a surfactant or detergent, and water to wet, emulsify, or reduce surface tension. Cleaning removes large numbers of microorganisms from surfaces. Cleaning precedes disinfecting on surfaces and helps to ensure the effectiveness of the subsequent disinfection step.
- Terminal cleaning (after patient discharge) of a room or area involves both cleaning and disinfection. Terminal cleaning is particularly important when a room has been occupied by someone harboring a pathogen associated with HAIs—e.g., MRSA, *C. difficile*, VRE—because patients newly admitted to a room previously occupied by someone with a MDRO or *C. difficile* up to three weeks earlier are at increased risk of acquiring those pathogens. Terminal cleaning must include, at a minimum, cleaning and disinfection of surfaces touched by patients, staff, and visitors. All environmental surfaces must be cleaned followed by disinfection in accordance with standards. If a room includes linens and privacy curtains, they should be replaced.

General framework and design of intervention programs: horizontal vs. vertical

The most effective design of integrated programs to prevent, identify through surveillance, and control HAIs is somewhat controversial.[36] Broad strategies that attempt to reduce all infections due to all pathogens are sometimes called "horizontal". Narrower strategies aimed at select pathogens or a single anatomic site are called "vertical." For example, some infectious disease specialists have recommended widespread screening for MRSA asymptomatic carriers in an attempt to reduce the likelihood of MRSA-related HAIs. But in a 2010 paper, hospital epidemiologists and infectious disease specialists Wenzell and Edmond make a strong case for horizontal programs as being far more efficacious than vertical programs, although they acknowledge value in screening some patients for certain organisms and treating asymptomatic carriers prior to specific procedures.

In the same paper, the authors observed that many studies influencing the design of infection control bundles are not based on randomized controlled trials but rather on observational cohort studies. These would generally be judged as less reliable (evidence level B, using AHRQ criteria). These authors and others recognize that RCTs are not always feasible because of the complexities of medical care and regularly changing circumstances within a hospital. Edmond has also pointed out, however, that the drive to completely eliminate HAIs and the belief that it is even possible have been fostered, in part, by sub-optimal evidence—evidence that is weak, flawed, or even absent.[37] What works or at least contributes to reduced incidence of HAIs? What's the evidence? These will always remain key questions as new interventions are proposed.

Hand hygiene

The importance of hand hygiene in preventing the transmission of HAIs has been recognized since the 19th century and is indispensable to effective infection control practices. Since 2002, the cornerstone of hand hygiene involves use of alcohol-based handrubs, provided that hands have previously been cleaned with soap and water.

What does "antimicrobial" mean?

- An antimicrobial product can have a range of effects on microbial growth that vary from weak to strong.
- Weak -> strong effects: Slows the rate of microbial growth -> stops growth -> kills some percent of microbes over time -> kills some percent of microbes quickly (e.g., < 10 min.) -> kills all microbes, including spore-formers quickly.
- When choosing products because of "antimicrobial" properties, purchasers should have access to sufficiently detailed information to know what kinds of antimicrobial effects have been demonstrated as well as risks and tradeoffs associated with their use.

Alcohol-based handrubs are more effective and efficient as decontaminants than regular or antimicrobial soaps and water. In the United States, antiseptic handwash products intended for use by health care workers are regulated by the Food and Drug Administration's (FDA) Division of Over-the-Counter Drug Products (OTC). Requirements for in vitro and in vivo testing of health care worker handwash products and surgical hand scrubs are outlined in the FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products (TFM).[38] This 1994 monograph is currently undergoing revision and the FDA is proposing to establish new conditions under which OTC health care antiseptic active ingredients are generally recognized as safe and effective (GRAS/GRAE) based on FDA's reevaluation of the safety and effectiveness data requirements proposed in the 1994 TFM.[iii] The public comment period ended in October 2015.

See appendix B for definitions and status of various hand hygiene products.

[iii]The draft revision of the FDA TFM is available here http://www.regulations.gov/#!documentDetail;D=FDA-2015-N-0101-0001.

Cleaning and disinfection

The CDC's cleaning and disinfection guidelines distinguish among critical, semicritical, and noncritical items:

- Critical items are purposely introduced into the patient—for example, the diagnostic or therapeutic use of medical devices or surgical instruments.
- Semicritical items may come in contact with non-intact skin or mucous membranes from time to time.
- Noncritical items are those that come in contact with intact skin but not mucous membranes.

The guidelines further divide noncritical items into noncritical patient care items and noncritical environmental surfaces. Examples of noncritical patient care items are bedpans, blood pressure cuffs, crutches, and computers. Noncritical environmental surfaces include bed rails, some food utensils, bedside tables, patient furniture, and floors. Noncritical environmental surfaces frequently touched by hand (e.g., bedside tables, bed rails) potentially could contribute to secondary transmission by contaminating hands of health-care workers or by contacting medical equipment that subsequently contacts patients.

Despite evidence that many noncritical high-touch surfaces can harbor pathogens responsible for HAIs, studies show that their cleaning can be highly variable within and among hospitals.[39] Compliance with cleaning and disinfection guidelines is an ongoing challenge to environmental services departments and direct care providers who also have responsibility for cleaning and disinfection of surfaces and devices.

Various standards have been proposed to judge the adequacy of cleaning and disinfection.[45] The US Department of Agriculture recommends that microbial counts on food-processing equipment should be <5 colony-forming units (CFU)/cm^2 before plant start-up, and some infectious disease specialists conclude that this is a reasonable standard to apply to noncritical surfaces in hospitals that are subject to cleaning and disinfection guidelines. According to this proposal, finding more than 5 CFU/cm2 on a hand contact surface indicates that there might be an increased risk of infection for the patient and should generate an evaluation of the cleaning and disinfection practices for that surface. This is based on three defensible suppositions: 1) an increased total microbial burden, irrespective of what the organisms are, implies insufficient cleaning, which would increase the chance of a pathogen that can cause disease being present, 2) a heavy microbial burden may mask finding a pathogen, and 3) a heavy microbial burden increases the chance that a pathogen is present.

Whereas the disinfectant efficacy and limits of the specific products identified by the CDC are fairly well known when they are properly used, some of them have hazardous properties that can pose risks to health care personnel. A recent publication from the Cleaning and Disinfecting in Healthcare Working Group of the National Institute for Occupational Safety and Health, National Occupational Research Agenda (NIOSH/NORA Working Group) focused on risks to the respiratory health of health care personnel who may be exposed to chemical agents during cleaning and disinfection of noncritical items and surfaces.[46] Some are known to be respiratory irritants or allergens and can cause or exacerbate asthma. The objective of the Working Group was to provide a more integrated approach to effective environmental surface cleaning and disinfection while protecting the respiratory health of health care personnel.

The Working Group noted that hospital purchasers may be required by their institutional standards to purchase only products approved and registered by the US Environmental Protection Agency (EPA). EPA-approved disinfectants typically require a human health risk assessment of the active ingredients, but asthma is not an endpoint examined under EPA protocols. And, so-called "greener" cleaning products with fewer hazardous properties may not have undergone standardized evaluations and be registered as disinfectants by EPA, leaving purchasers with limited options.

The NIOSH/NORA Working Group concluded with a call for more research into greener alternatives to hazardous disinfectants, improved hazard communication, and more systematic evaluation of emerging non-chemical technologies such as UV light and products made of materials with antimicrobial properties. The latter are discussed in more detail below.

Environmental surfaces

Contaminated environmental surfaces are important potential links in the transmission pathway of pathogens from one person to another.[47] Microbes are able to colonize virtually any surface and can persist for weeks on materials commonly used in hospitals including stainless steel and various plastic polymers. MRSA can persist on surfaces for more than six months.[48, 49] Spore-forming *C. difficile* can also persist for up to a year or more.[50] These surfaces can be a source of microbes with the potential to be transmitted without regular cleaning and disinfection.[51]

Current guidelines recommend that surfaces in patient rooms be cleaned and disinfected routinely (e.g., daily or three times weekly) and when a patient is moved or discharged from the room (terminal cleaning).[52] High-touch surfaces, such as doorknobs, bed rails, over-bed tables, call buttons, IV poles, and surfaces in and around toilets, probably play a role more frequently in microbial transmission than lower-touch surfaces even though studies show that the microbial load on high-touch surfaces is only slightly higher before cleaning and disinfection than lower-touch surfaces.[53]

Given the persistent problem of HAIs despite existing infection control programs, interest in development and deployment of antimicrobial technologies built into materials on high-touch and other surfaces in hospitals is growing. It is based on two observations: 1) environmental surfaces can harbor pathogens for long periods of time, and 2) cleaning and disinfection of surfaces is often inadequate. It is also based on a presumption that has rarely been verified: that regularly reducing surface microbial load below a certain level by methods in addition to standardized cleaning and disinfection practices will reduce the risk of transmission of pathogens by health care workers or others, thereby reducing the incidence of HAIs.

From CDC's Guidelines for Cleaning and Disinfecting

Agents suitable for use to disinfect noncritical, semicritical, and critical items or surfaces:

Low level disinfectants: may be used for noncritical items

- Ethyl or isopropyl alcohol
- Sodium hypochlorite
- Phenolic germicidal detergent solution
- Iodophor germicidal detergent solution
- Quaternary ammonium germicidal detergent solution

Intermediate level disinfectants:

- Ethyl or isopropyl alcohol
- Sodium hypochlorite
- Phenolic germicidal detergent solution
- Iodophor germicidal detergent solution

High level disinfectants: (for semicritical items; may come into contact with non-intact skin or mucous membranes)

- Glutaraldehyde-based formulations
- Ortho-phthalaldehyde (OPA)
- Hydrogen peroxide 7.5 percent
- Hydrogen peroxide and peracetic acid
- Wet pasteurization at 70 degrees C for 30 minutes with detergent cleaning
- Hypochlorite, single use chlorine generated on-site by electrolyzing saline containing >650-675 ppm active free chlorine

Newer methods for terminal cleaning and disinfecting rooms—no touch disinfection:

- Micro-condensation hydrogen peroxide vapor: Hydrogen peroxide vapor (HPV) decontamination is a sporicidal vapor-phase method that inactivates a range of hospital pathogens including on surfaces that are difficult to clean. HPV is used to eliminate environmental reservoirs contributing to multidrug-resistant organism (MDRO) outbreaks, and regular use of HPV to decontaminate rooms of patients with drug resistant organisms has significantly reduced the incidence of *C. difficile* infection and VRE in some settings when used after terminal cleaning. [40, 41, 42]
- Hydrogen peroxide dry mist system
- Gaseous ozone
- Alcohol/quaternary ammonium power sanitizing system
- Ultraviolet germicidal irradiation (UVGI) room decontamination: This technology can also be used after terminal cleaning [43, 44]

Antimicrobials in products: material preservation vs. pathogen reduction

Antimicrobials can be added to materials and products for two general reasons. First, many materials and products, including wood, polymers, adhesives, foams, and fabrics, are susceptible to damage from microorganisms that can thrive on imbedded nutrients. Because of this, biocides are frequently added to protect the material from degradation and prevent stain and odor from microbial contamination during product use. Second, antimicrobials may be added to a product—or a product may be manufactured from materials with antimicrobial properties—in order to reduce microbial colonization with human pathogens. If this rationale is claimed or implied by a manufacturer, the EPA considers it a health-related claim, and it carries with it a burden to examine the safety and efficacy of the agent or material in greater detail than if it is used solely for material preservation.

In the European Union, under the Biocidal Product Regulation (BPR), a biocide is defined as a chemical substance or microorganism intended to destroy, deter, render harmless, or exert a controlling effect on any harmful organism by chemical or biological means. The BPR requires registration of active ingredients and once registered, biocides must undergo a testing and review process, regardless of the purpose of their use.

In the United States, the EPA defines biocides as "a diverse group of poisonous substances including preservatives, insecticides, disinfectants, and pesticides used for the control of organisms that are harmful to human or animal health or that cause damage to natural or manufactured products". The two definitions are similar, although the EPA definition includes plant protection products and some veterinary medicines. Thus, a biocide can be a pesticide, including fungicides, herbicides, insecticides, algicides, molluscicides, miticides, and rodenticides, as well as antimicrobials, including germicides, antibiotics, antibacterials, antivirals, antifungals, antiprotozoals, and antiparasites.

Additionally within the United States, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes and requires federal regulation of the distribution, sale, and use of pesticides to protect human health and the environment. Products that kill or repel bacteria or germs are considered pesticides, and must be registered with the EPA prior to distribution or sale. The EPA will not register a pesticide until it has been tested to show that it will not pose an unreasonable risk when used according to the directions. This includes pesticides used on textiles to provide antimicrobial or other pesticidal characteristics. FIFRA does not allow companies to make public health pesticidal claims for any product distributed or sold unless the product has been approved and registered by the EPA or is covered by an exemption from registration. The EPA will take action against companies that make such claims. Additionally, the EPA must also approve wording of health-related claims for products that have undergone full evaluation and registration under FIFRA.

Importantly, however, in the United States,, under a "Treated Articles Exemption" of FIFRA, companies can avoid a lengthy pesticide registration process if they refrain from making explicit or implicit health benefit claims about the antimicrobial product and make clear to customers that the biocide, if it is mentioned at all, is solely for protection of the treated article.[54, 55] As a result, products containing biocides that are exempted under this provision do not need to be evaluated for human health or environmental impacts, nor do they need to be evaluated for efficacy in reducing surface microbial load and potential for the article to serve as a source or reservoir for pathogens responsible for HAIs.

Antimicrobials that are added to a product for the preservation of the material are often not identified to distributors or consumers and in such cases their presence is unknown. However, in some cases, the antimicrobial is clearly identified and marketed for contributing stain- or odor-control properties to the product. If a treated article exemption is claimed under FIFRA, the manufacturer is prohibited from making any health-related statements about the product, but despite these marketing limitations, customers often make the assumption that if microorganisms are less likely to grow on the surface of a product then people touching the surface will be less likely to come in contact with them. It seems likely that this assumption underlies much of the growing consumer interest in products with antimicrobial properties.[56]

The FDA regulates medical devices and antimicrobials added to medical devices for purposes of reducing infection risk.[57] These will not be further considered in this paper. The FDA also regulates chemical sterilants and high-level disinfectants described above and used for processing semicritical devices.

Antimicrobials in hospital furnishings

Integrated efforts involving surveillance, rigorous hand hygiene, and cleaning and disinfection according to guidelines are proven methods for preventing and controlling HAIs. Yet, strict adherence to guidelines at all times is challenging and some facilities are looking at newer technologies to see if they add value to ongoing efforts. Among them is the addition of antimicrobials not only to medical devices that may come in contact with blood or mucous membranes but also to furnishings and building products with surfaces that may become contaminated with pathogens and aid infectious disease transmission. Surfaces on products and materials in patient care areas are of particular interest because they can provide a reservoir for pathogens along the transmission pathway from one person to another.

Most antimicrobial fabrics and solid materials on the market today contain agents that inhibit growth or kill some percentage of microorganisms over long periods of time but only do so under certain circumstances. Due to this, most antimicrobial-containing products perform at a level that may be useful for aesthetic purposes, including odor control, and material protection but not necessarily for infection control.[58] Few antimicrobial fabrics, for example, kill appreciable percentages of microorganisms quickly (i.e., in less than 10 minutes.) Such antimicrobial activity is roughly equivalent to that which would be brought about by the use of a low-level disinfectant. Manufacturers adding antimicrobials to fabrics may advertise them as helping to control odor and preserve the material and still qualify for a "treated article exemption", but if they make claims about reducing microbial colonization it can be considered a health-related claim requiring full FIFRA evaluation and registration.

Microbiological tests used to characterize the efficacy of antimicrobial-containing products vary and are at the discretion of the companies undertaking them, since EPA does not review these data when a treated article exemption is claimed and substantiated. In general, the methods commonly used to test antimicrobial properties of fabrics and solid products are designed to detect low-level activity over long periods of time, in contrast to the methods used to test disinfectants, which look for high-level activity over short periods of time. Most of the commonly used antimicrobial test methods for fabrics, plastics, and other solid materials do not have standardized success criteria at all. In other words, interpretation of the test results is entirely up to whomever is interested.

A variety of protocols for evaluating the efficacy of antimicrobials added to fabrics, plastics, and other solid non-medical products, including methods AATCC 147, AATCC 100, ASTM E2149, JIS l 1902 and JIS Z 2801, and their strengths and weaknesses are summarized in Appendix C. It is important to note that these are laboratory methods and not evaluations of efficacy in clinical settings where products may be used.

Summaries Of Antimicrobials: The Approaches

Antimicrobial coatings and surface technologies

A variety of antimicrobial additives and coating technologies are currently available and more are in development.[59] In general, the antimicrobials fall into two categories: leaching and non-leaching. Those that leach during use will lose their effectiveness over varying time periods. Antimicrobials bound to the material are less likely to leach and their effectiveness may be prolonged.

Textured surface: Sharklet™

Sharklet™ textured film uses a very fine micron-scale pattern, inspired by the micro-topography of shark skin, which reduces microbial adhesion.[60] It does not involve any chemical antimicrobial additives. When applied to high-touch surfaces it can help reduce microbial load between cleanings. This technology has not been studied in clinical settings to evaluate whether or not it helps to reduce HAIs.

Chlorinated organic antimicrobials

Triclosan

For many years, triclosan (5-chloro-2-(2,4-dichlorophenoxy)-phenol) has been added to various kinds of hand soap, toothpaste, mouthwashes, touch surfaces, lunchboxes, kitchen items, toys, plastics, and clothing from which it is released and functions as an antimicrobial agent.[61] Triclosan is generally more effective against gram-positive than gram-negative bacteria.[62] Triclosan acts by inhibiting an enzyme necessary for synthesizing fatty acids, which are necessary for building cell membranes and for cell division.[63]

Studies show that bacteria can have both natural and acquired mechanisms of resistance to triclosan.[64] The primary mechanism of acquired resistance is due to mutations within the coding region of the enzyme necessary for fatty acid synthesis, making triclosan less effective. Other mechanisms include production of an enzyme that degrades triclosan and efflux pumps within bacteria that actively remove the chemical from the cell. Some studies, but not all, show that bacteria that become resistant to triclosan can also become resistant to other antibiotics.[65, 66]

Exposures to triclosan are widespread in the general population through both oral and transdermal pathways.[67] Triclosan residues are measureable in adult and infant urine, breast milk, and meconium.[68] Use of triclosan-containing toothpaste or hand soaps significantly increase urinary triclosan levels.[69] Some triclosan discharged to waste water passes through wastewater treatment plants and is released in surface water and sludge. Triclosan can persist in the environment and contaminate fish and even food grown in sludge-amended soil.[70, 71]

The safety of triclosan exposures is undergoing increased scrutiny as studies show an increasing number of potentially adverse effects in laboratory animals, wildlife, and to some extent humans. Triclosan has effects on the thyroid, estrogen, and testosterone systems in several animal species, including mammals.[72, 73, 74, 75, 76] These effects are of particular concern when exposures occur during developmental windows of susceptibility, and their impacts on brain and reproductive system development have not been adequately evaluated. Triclosan exposure can also impair muscle function in animal models and has been associated with hay fever or allergies in humans.[77, 78, 79, 80]

The topical Over-the-Counter Drug Monograph of the FDA, drafted in 1974 and never finalized, finds existing data insufficient to classify triclosan as either safe or effective. Now attempting to finalize the document, the agency's current draft continues to find existing data insufficient to classify triclosan as either safe or effective.

The 2014 Society for Healthcare Epidemiology of America (SHEA) Compendium on Hand Hygiene advises against the use of triclosan-containing soap in health care facilities because of lack of evidence of superior clinical effectiveness compared to other products, concern about promoting antibiotic resistance, widespread human exposures, and potential adverse health effects.[81]

In summary, triclosan has not been shown to be effective in a number of applications as an antimicrobial

in consumer products, can increase the risk of more generalized antibiotic resistance, and can have adverse health effects in several animal species, including mammals, with documented evidence of widespread exposure in the general human population.

Triclocarban

Triclocarban (3,4,4'-Trichlorocarbanilide) is another chlorinated organic compound with widespread use similar to triclosan. Triclocarban is also environmentally persistent, detectable in many rivers and streams, and tends to bioaccumulate in many invertebrates. [82] Triclocarban shares a number of toxic properties with triclosan, including hormonal effects. Although in 1994 the FDA proposed to classify triclocarban as "generally recognized as being safe" (GRAS) for all health care uses, new data and concerns have led the agency to propose now that data are insufficient to classify triclocarban as safe or effective. Data gaps include information on dermal absorption, dermal carcinogenicity, hormonal effects, and promotion of antibiotic resistance.[83]

Metallic compounds

Silver

Broad-spectrum antimicrobial properties of silver have long been recognized and led to uses in water and air purification, food production, cosmetics, medical applications, textiles, clothing, and many household products.[84] Global production of textiles with antimicrobial properties, including added silver, was estimated at 100,000 tons in 2000 with rapid annual growth.[85] In health-care, silver-containing preparations are used to prevent infections in burns, traumatic wounds, and diabetic ulcers. Urinary and vascular catheters and other devices are sometimes impregnated with silver compounds to reduce the risk of infection.

Various technologies employ metallic silver, silver salts, silver-polymer composites, silver-impregnated zeolites (microporous, aluminosilicate minerals commonly used as commercial adsorbents and catalysts) or silver nanoparticles (clusters of silver atoms with at least one dimension measuring 1-100 nm). Concentrations of silver in textiles can vary widely from 2-3000 mg/kg (ppm).[86, 87] Depending on how it is deployed, silver can be effective

Case Study: silver-zeolite

A silver-zeolite matrix[92, 93] (2.5 percent [w/w] silver, 14 percent zinc) coating on stainless steel coupons was tested for antimicrobial activity against *E. coli, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Listeria monocytogenes* in petri dishes and broth suspensions using standardized assays. In broth cultures, the authors reported a 5 $\log_{10}$ reduction in S aureus and 3.6 $\log_{10}$ reduction of E Coli in 6 hours and 4-5 $\log_{10}$ reduction of all species at 24 hours.[94] On silver-powder coated cups, 5.5 $\log_{10}$ reduction of *E. coli* and *L. monocytogenes* at 4 hours was reported. On stainless steel surfaces coated with paint containing the silver-zeolite matrix, at 250 C and 80 percent relative humidity, the viability of spores of *Bacillus anthracis, B. cereus,* and *B. subtilis* was not affected.[95]

Another study examined the antibacterial efficacy of the same silver-zeolite matrix coating when applied to door handles across a college campus. Twenty-five handles were coated with a powder containing the silver-zeolite and 25 control handles were coated with the same powder but without the silver.[96] Door handles were sampled for 6-week periods in both the fall and spring semester over three years, and bacteria were cultured and counted on tryptic soy agar (TSA), MacConkey agar (MAC), and mannitol salt agar (MSA). Semester-averaged bacterial counts cultured from silver-coated door handles were significantly lower than those from control handles after three years. However, some bacteria were consistently isolated from all door handles, including those that were silver-coated, suggesting that the silver zeolite was only partially effective against some bacterial populations. Moreover, there were instances within each semester when more bacteria were obtained from silver-coated door handles than control-coated door handles or the differences between the two were minimal. In many of these instances, bacterial growth was isolated predominantly on TSA plates with minimal to no growth on the other two plates. TSA agar supports the growth of a range of different gram-positive and gram-negative bacteria, while MSA supports primarily gram-positive *S. aureus,* and MAC supports primarily gram-negative bacteria. The results suggest that, at times, gram-positive bacteria other than *S. aureus* are maintained on the silver-coated door handles.

against a wide range of microorganisms, including gram-positive and gram-negative bacteria, fungi, viruses, yeast, and algae.[88]

Silver-containing environmental surfaces and textiles in health care settings are increasingly promoted as products that may help reduce HAIs by reducing microbial loads as demonstrated in laboratory studies or environmental microbiological testing.[89, 90] However, no evidence demonstrates that these products actually help reduce HAIs.

Mechanisms Of Antimicrobial Action

Multiple mechanisms probably underlie the antimicrobial activity of silver but not all are fully understood and some are controversial.[97, 98] Binding with disulfide and sulfhydryl groups in the proteins of cell walls, cell membrane disruption and uptake of free silver ions through the cell membrane followed by disruption of energy production and DNA replication, and generation of reactive oxygen species (ROS) with cellular and DNA damage have all been reported to varying degrees.[99]

The antimicrobial action of silver appears to vary with the nature of the silver compound and particle size. Most forms of silver depend to a large extent on the release of silver ions for their antimicrobial activity.[100] This is facilitated by the presence of oxygen. Microbes take up oxidized silver ions. Higher initial concentrations of silver ions are more effective. Silver ion release is also temperature dependent with higher amounts released at higher temperatures. The antimicrobial properties of silver also vary with relative humidity (RH), but the relationship may not be monotonic. One study shows higher activity at 90 percent compared to 22 percent RH, while another shows higher activity at 40 percent compared to 90 percent RH. [101, 102]

Nanosilver particles also depend largely on ion release for antimicrobial activity. However, there is also evidence that in the presence of oxygen, nanosilver particles themselves can induce generation of ROS.[103, 104] When extremely small silver particles are added to a product for antimicrobial purposes, silver ion release from the material containing nanosilver particles is greater and more effective than from material containing microsilver particles because of the larger surface area of the nanoparticles.[105] Newly developed silver-polymer composites generally rely on incorporating silver nanoparticles for enhanced antimicrobial properties.[106, 107]

Over time, depending on the nature of the silver-containing material, the reservoir of silver can become depleted and antimicrobial activity diminished. This can readily occur with laundering when silver is incorporated into textile fibers but can be slowed with extended-release technologies that bind the agent more strongly to the fibers.[108] However, if silver is too tightly bound to textile fibers it may not be released in amounts sufficient for antimicrobial activity.[109] Polymers that release oxidized silver ions can act as reservoirs, shedding them into the immediate environment over extended periods.

Microbial resistance to silver

Microbial resistance to silver is well known although there is little consensus about its clinical or public health importance. Evidence of acquired silver resistance seems to relate mostly to gram-negative and not gram-positive bacteria. The main mechanisms of resistance involve reducing ionic silver penetration into a cell via a transporter in the cell membrane, reducing accumulation via an efflux pump, and reducing toxicity by reduction of ionic silver to a less active metallic form. Silver resistance can also be genetically coded on chromosomes or in plasmids transferrable to other bacteria. [110, 111, 112]

Case Study: Silver ion BioCote®

In one study of a silver ion antimicrobial product (BioCote®) in a clinical setting, cultures obtained from multiple treated surfaces showed 68 percent (fabrics) – 98 percent (laminates) reduction in aerobic colony-forming units (CFUs) from surfaces in an outpatient treatment unit with treated products compared to a unit without treated products.[91] Treated products included doors, safety rails, electric switches, cubicle curtains, window blinds, and furniture fabric. Evaluation of microbial contamination began 12 months after treated items were put into use. The study description does not include information about the timing of swabbing surfaces for sampling as related to timing of cleaning and disinfection. No attempt was made to identify bacteria by species or to study impacts on HAIs.

Plasmid-derived silver resistance is a concern since this kind of metal resistance is associated with more general microbial resistance to antibiotics used therapeutically.[113] This is particularly important as use of silver in medical products, devices, and hospital surfaces and textiles becomes more widespread. Evidence of bacteria that are resistant to silver in hospitals has been reported, and there is concern that more rapid emergence of silver resistant bacteria would interfere with therapeutic uses of silver in burn and wound care.[114] Recent studies show that some pathogenic gram-negative bacteria can acquire silver resistance with relative ease, leading to calls for more active surveillance to detect the emergence of silver-resistant organisms and greater control over the use of silver for medical and non-medical applications to help limit the further development of resistant organisms.[115]

Silver toxicity

Silver in various forms, including nanosilver particles, may be released to the environment during product manufacture, use, and disposal. Silver impregnated into textiles and other consumer products can be worn away through laundering, cleaning, and abrasion and released into the environment over varying time periods, depending on concentrations and bonding technologies. Wash water from laundering silver-containing textiles is discharged to waste water treatment plants, where there is the potential for adverse impacts on microorganisms necessary for processing organic material in sewage.[116] Studies show that most silver is sequestered in sewage sludge in the form of insoluble silver sulfide and not released in water effluent from treatment plants. However, land application of sewage sludge enables more general environmental releases, including into surface waters.[117, 118, 119]

Human health risks associated with metallic or ionic silver exposure through the skin, gastrointestinal tract, or lungs are relatively low.[120] The main effects from long-term silver exposure are argyria, a blue-gray discoloration of the skin, and agyrosis, a blue-gray discoloration of the corneas and conjunctiva.

Human health risks from exposure to nanosilver particles are less well-studied. In particular, occupational exposures to nanosilver particles through inhalation or ingestion may be of unique concern because of tissue distribution and toxic properties related to particle size as well as chemical composition.[121] Laboratory studies in rodents show that silver nanoparticles can accumulate in and damage tissues such as the liver, lungs, and brain.[122, 123, 124 125, 126] A recent review concluded that current knowledge of the human health hazard of nanosilver is limited.[127] In general, unique properties of nanoparticles related to their size and configurations create challenges for assessing risks resulting from exposure in workers, consumers, and ecosystems.[128]

Silver is highly toxic to many aquatic organisms. A recent review has summarized data from numerous studies submitted for product registration under provisions of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program in the European Union.[129] Silver nanoparticles and silver salts are categorized as extremely toxic or very toxic[iv] to crustaceans, algae, and fish. However, silver toxicity may be reduced when it forms complexes with other molecules or materials in the environment.[130]

A recent analysis of environmental risks associated with nanosilver particles in textiles recommends that potential release during washing should be determined before marketing and use.[131] This would undoubtedly be a valid recommendation for all forms of silver in textiles.

Copper

Antimicrobial properties of copper have been known for centuries, and various copper alloys are now registered by the EPA as antimicrobial agents. Their copper content ranges from 60-90 percent. Registration of a copper alloy allows the registrant to market its product with a claim that, when used in accordance with the label, it "kills 99.9 percent of bacteria within two hours" (3 $\log_{10}$ reduction).[132] The agency concluded that "the use of these products could provide a benefit as a supplement to existing infection control measures" and emphasizes "the importance of continuing to practice appropriate infection control measures diligently."

The EPA's protocol for evaluating bactericidal activity of copper alloy surfaces requires evaluation of efficacy of the product against *Staphylococcus aureus, Enterobacter*

[iv] Concentration of agent associated with 50 percent lethality in test organism < 1 mg/L. For silver nanoparticles, this concentration is 0.01 mg/L for crustaceans (very toxic). For silver salts, this concentration is 0.001 mg/L for crustaceans (extremely toxic)

aerogenes, and *Pseudomonas aeruginosa* and adequate resistance to abrasion and chemical exposures.[133] An effective product is expected to achieve a 3 $\log_{10}$ reduction in bacterial load.

Copper surfaces and microbial load

In a cross-over design study on an acute medical ward in a hospital in the UK, three copper containing items; a toilet seat (coated with a pure copper/resin composite,70 percent Cu); a set of brass tap handles (60 percent Cu) and a brass door push plate (70 percent Cu) were sampled for microbial contamination and compared to equivalent items with plastic, chrome-plated, and aluminum surfaces, respectively. [134] Median numbers of aerobic CFUs were 90-100 percent lower on the copper-containing surfaces. No *C. difficile* or MRSA was isolated from any surface. No methicillin-sensitive *S. aureus* (MSSA), VRE, or *E. coli* were isolated from a copper-containing surface while each was occasionally isolated from a control surface.

Other hospital studies have also reported significantly reduced microbial load on door knobs, push plates, light switches, over-bed tables, and other high-touch surfaces made of copper alloys compared to those made of other metals or plastic.[135, 136, 137]

A study in an outpatient phlebotomy office compared the microbial load on chair arms and trays with and without copper surfaces. [138] Swabs from surfaces showed 90 percent reduction in aerobic CFUs from trays and arms with copper alloy (90 percent copper, 10 percent nickel) compared to chairs with wooden arms and plastic composite trays. Both kinds of surfaces were wiped down with a quaternary ammonium compound at the end of each day. Cultures were obtained during the mid-afternoon.

Copper surfaces and healthcare-associated infections

The first and only published study examining the association between copper surfaces and HAIs was carried out in three hospital intensive care units.[139] Six high-touch objects—bed rails, over-bed tables, IV poles, visitor chair arms, nurses call button, and computer mouse—were made of copper alloys and used in the treatment arm of the trial. HAIs and/or colonization with MRSA or VRE were tracked in patients in rooms where these objects were mostly used and compared to outcomes in patients where these objects did not contain copper. HAIs and/or colonization (either or both events considered together in one group for statistical analysis) were significantly lower in patients cared for in rooms with the copper-containing objects.

In response to this study, in a letter to the editor of the journal, Harbarth et al. pointed out that the study authors, Salgado et al., had not analyzed their data for the association between any HAI (i.e., as one group, with or without colonization) and treatment in a room with copper-containing items.[140] That, Harbarth et al. point out, would be most clinically relevant. When that analysis is done, it fails to show a significant association. Salgado et al. respond that their study was not powered to study that association and conclude that when the bacterial burden is reduced in the vicinity of the patient, infection rates were lower.[141] A recent systematic review and meta-analysis concludes that the GRADE quality of evidence in this study is low based on the high risk of bias due to the absence of appropriate randomization and incomplete blinding.[142]

Copper in textiles

Copper can be added to textile fibers through a plating process or added to a polymer mix of synthetic fibers to create textiles with antimicrobial properties.[143] Increasingly, copper nanoparticles, sometimes encapsulated, combined with carbon nanotubes, or added to polymers in other formulations, are being used in textile manufacture as antimicrobials. In general, nanoparticles can enhance antimicrobial properties, water repellence, soil resistance, antistatic, anti-infrared, and flame-retardant properties of conventional textiles.[144]

The antimicrobial efficacy of textiles containing copper or other antimicrobial agents can vary considerably and interpretation of results of laboratory testing is subjective (see appendix C). As with all added antimicrobials, there will always be a risk that purchasers and users of textiles marketed as having antimicrobial properties will not fully understand the limits of their performance.

A study in a long-term brain injury ward in an Israeli hospital examined HAIs, antibiotic use, and patient-days with fever over two six-month periods.[145] During the first period, regular linens were used in the ward. During the second period, all bed sheets, pillowcases, patient

shirts, patient pants, patient gowns, towels, underpads, and personal robes were replaced with copper oxide-impregnated products—the colors of which were different from standard supplies. Laundering and infection control measures were the same during each period. The authors reported a 24 percent reduction in HAIs per 1000 hospitalization-days, a 47 percent reduction in the number of fever days per 1000 hospitalization-days, and a 33 percent reduction in total number of days of antibiotic administration per 1000 hospitalization-days during the second period. A critique of this study concludes that this evidence is of very-low GRADE quality due to its uncontrolled before-after design.[146]

Mechanisms of copper antimicrobial effects

Antimicrobial effects of copper probably result to a large extent from: 1) release of copper cations from the metal surface, 2) its tendency to alternate between its cuprous [Cu(I)] and cupric [Cu(II)] oxidations states causing combinations of membrane damage, and 3) accumulation of copper in cells, with some degree of oxidative stress and DNA damage, depending on contact time.[147, 148, 149] Killing begins quickly and persists. Copper nanoparticles can also enter microbial cells. Dry copper surfaces are effective at a range of temperatures and humidity levels.[150, 151] Dry copper surfaces do not depend exclusively on the release of copper ions for antimicrobial properties and probably directly damage microbial cell membranes with a cascade of downstream events including DNA damage.[152]

Copper resistance

Antimicrobial resistance to copper has been studied fairly extensively, although the mechanisms are not fully understood. Since many coins are made of copper alloys, cultures obtained from their surfaces are a ready source of bacteria that are resistant to dry copper surfaces, although it should be noted that the bacterial load on copper coins is much smaller than on paper currency. In one study, the majority of isolates from copper coin surfaces were gram-positive.[153] The largest number were staphylococci, followed by micrococci, and bacilli. A smaller number were gram-negative. Interestingly, when these isolates that were obtained from dry copper surfaces were tested on moist copper surfaces, some were as sensitive as strains without any copper resistance at all. This suggests at least partially different mechanisms of toxicity on dry compared to moist copper surfaces.[154]

Copper toxicity

Copper is an indispensable element of aerobic metabolism that works as a cofactor in various essential biologic reactions in many organisms, including humans. But it can have adverse effects at excessive concentrations. Normally copper homeostasis is fairly tightly controlled by decreased absorption or increased excretion of excessive dietary levels. But copper toxicity may result from excessive levels caused by accidental or occupational exposures, environmental contamination, adrenal insufficiency, and inborn errors of metabolism (e.g., Wilson's disease).

Copper intake varies with dietary as well as environmental factors.[155] Most diets contain enough to prevent a deficiency and not enough to cause toxicity. In the United States, the Institute of Medicine recommends intake of 0.9 mg Cu/d for adults, while the tolerable upper level is 10 mg/d. The EPA has established the maximum contaminant level goals for Cu at 1.3 mg/L in drinking water.

Toxicity resulting from excessive copper exposure or accumulation is generally thought to result from free-radical induced oxidative damage, although additional mechanisms have been proposed. These include altered lipid metabolism, altered gene expression, and abnormal protein folding with aggregates like those seen in some neurodegenerative diseases.[156]

With increasingly widespread use of engineered nanomaterials, human and ecosystem effects associated with exposure is of great interest but not fully understood.[157] Copper nanoparticles are more readily absorbed from the intestinal tract and widely distributed in many tissues. Presumably their higher surface area/volume ratio contributes to increased toxicity by producing a higher concentration of copper ions in target tissues.

As with other engineered nanomaterials, copper nanoparticles may pose risks that differ from those associated with other forms of the metal, depending on particle size and route of exposure. For example, the toxicity profile of Cu nanoparticles differs from that of larger Cu particles and is similar to that of copper ions in in vivo toxicity testing in rodents exposed by oral gavage.[158] Kidney, liver, and spleen showed much greater pathology after exposure to Cu nanoparticles at lower doses than

macroparticles. Inhalation of copper nanoparticles causes increased inflammation, oxidative stress, and cytotoxicity.[159, 160]

Copper salts and copper oxide nanoparticles are also toxic or very toxic to aquatic organisms, with the salts somewhat more potent in that regard.[161] However, silver salts and silver nanoparticles have greater aquatic toxicity than their copper counterparts at equivalent concentrations.

Zinc

Zinc is another metal with antimicrobial properties that is sometimes incorporated into textiles, surfaces, pigments, paints, cosmetics, and polymers such as polypropylene or polyethylene terephthalate in various formulations. Most applications now use zinc oxide nanoparticles (ZnO-NPs). Zinc and silver ions may be combined in a zeolite powder added to epoxy to coat solid surfaces in order to inhibit microbial growth.[162] When applied to stainless steel, its efficacy diminishes with repeated cleaning and scrubbing. Zinc pyrithione is an organic zinc compound in over-the-counter treatments for dandruff and seborrheic dermatitis.

Zinc compounds are anti-fungal and bacteriostatic. Antimicrobial properties of ZnO-NPs are attributed to oxidative stress and abrasion.[163] The oxidative effect results at least in part from absorption of photons from UV light, rearrangement of electrons, and generation of reactive oxygen species. But at least some antimicrobial effects are retained in the absence of light. There is some evidence that hydrogen peroxide is generated as an oxidant.[164] Most studies find antimicrobial activity against gram-positive and gram-negative bacteria, although it varies with nanoparticle preparation and details of final product manufacturing processes.[165]

Like silver and copper, zinc salts or Zn-NPs are toxic to aquatic organisms. Zn-NPs are more toxic to algae than Ag-NPs or Cu-NPs but less toxic to crustaceans.[166]

Antimicrobial polymers

Polyethylene glycol (PEG) coatings applied to solid surfaces in a several-step process during manufacture can help to prevent the adhesion of microbes and proteins.[167] Studies show that PEG-modified surfaces can effectively inhibit bacterial adhesion by up to 3 $\log_{10}$ unit reduction (10^3).

The term "antimicrobial polymers" refers to a class of polymers with variable ability to kill or inhibit the growth of microorganisms. These polymers are produced by attaching or inserting an active antimicrobial agent onto a polymer backbone or preparing a monomer with biocidal components and then polymerizing them or co-polymerizing them with another monomer. Sometimes inorganic agents like silver, copper, or titanium dioxide or an organic compound like triclosan are simply added to a polymer mix during processing, but the term "antimicrobial polymer" typically does not apply to this method or product.

The molecular weight and chain length of the polymer, as well as the electrical charge on the biocidal component, influence the strength of antimicrobial activity. Mechanistically, evidence suggests that positively-charged structures on an antimicrobial polymer attach to the negatively charged microbial membrane and disrupt its function, resulting in microbial death.

Antimicrobial polymers have been developed for many purposes, including fibers and textiles, medical devices, medical and dental composites, water filtration, food packaging, and household applications.

In a 2007 State of the Art Review, the authors note that the ideal antimicrobial polymer should 1) be easily and inexpensively synthesized, 2) be stable in long-term usage and storage at the temperature of its intended application, 3) not be soluble in water for a water disinfection application, 4) not decompose to and/or emit toxic products, 5) not be toxic or irritating to people handling it, 6) be regenerated upon loss of activity, and 7) be biocidal to a broad spectrum of pathogenic microorganisms in brief times of contact.[168] The field is rapidly growing and developing. The extent to which new products fulfil each of these criteria is often unknown or unreported. Examples of antimicrobial polymers used in fabrics and coatings include:

Chitosan: This is a naturally-occurring antimicrobial polymer; derived from chitin in the exoskeleton of crustaceans (e.g., shrimp, crabs) and some fungi. It is a broad-spectrum biocide sometimes used in cotton, wool, and synthetic textiles.

Synthetic nitrogen-containing polymers with inherent antimicrobial properties: Quaternary ammonium compounds, polyethyleneimine, polyguanidines. These can be grafted onto synthetic fabrics using a variety of techniques. Quaternary ammonium compounds have also been added to plastic polymer resins, paints, and coatings used in various applications.[169]

Recently Sherwin Williams developed a paint containing a quaternary ammonium compound (Alkyl (C14 50 percent, C16 10 percent, C12 40 percent) Dimethyl Benzyl Ammonium Chloride), which has been conditionally registered by the EPA and is permitted to claim to be "the first and only EPA-registered paint that continuously kills 99.9 percent of MRSA, *Enterobacter aerogenes, Staphylococcus aureus,* and Vancomycin resistant *Enterococci* (VRE) within 2 hours of exposure."[170] It is for "use on hard, non-porous interior ceilings, walls, doors, and trim in commercial, institutional, and residential rooms and on noncritical areas of hospitals." Painted surfaces "must be cleaned and disinfected according to standard practice. Health care facilities must maintain the product in accordance with infection control guidelines; users must continue to follow all current infection control practices, including those practices related to disinfection of environmental surfaces."

Organosilanes: Monomeric silicon chemicals are called silanes. A silane that contains at least one carbon-silicon bond (Si-C) structure is known as an organosilane. Surface coatings have been developed that combine quaternary ammonium molecules with a silane in order to impart antimicrobial properties. These can be applied to textiles or various hard surfaces where they form tight bonds, do not leach, and can last for prolonged periods of time. Two studies have examined the effectiveness of various organosilanes with added quaternary ammonium molecules in reducing the microbial load on surfaces in a healthcare setting. One study in an ICU demonstrated an average 2 $\log_{10}$ reduction in microbial contamination on bed rails, bed controls, tray tables, and walls above a sink eight weeks after all surfaces in the unit had been treated by spray application of the organosilane.[171] The other study in nine patient rooms on a rehabilitation ward found no significant reduction in microbial load on treated bedside rails, over-bed tables, television remotes, telephones, door handles, dressers, toilet seats, bathroom grab bars, and sink faucet handles over a four-week study period.[172] In this study, the organosilane was applied by microfiber cloths saturated with the product, which may have resulted in insufficient coating of surfaces.

Another wall coating (Lumacept™)[173] has been formulated using nanoscale oxides, polymer binders, and additives with structures that reflect UV light. A study of the antimicrobial effectiveness of a UV-C-emitting device in a hospital room experimentally contaminated with MRSA and *C. difficile* showed more rapid and complete decontamination of surfaces after UV-C treatment in a room with the wall coating compared to the same room with standard paint.[174]

Biguanide-based polymers: Polybiguanides kill microbes by electrostatic attractions occurring between the positively-charged biguanide groups and the negatively-charged bacterial cell wall. They can also be bound to a fabric surface using the same electrostatic interactions imparting antimicrobial activity.[175]

Halogen-containing polymers: e.g., *N*-halamines. These are heterocyclic organic compounds containing one or two halogen atoms (e.g., chlorine) covalently bound to nitrogen. *N*-halamines are active for a broad spectrum of bacteria, fungi, and viruses. Their antimicrobial properties are based on release of reactive Cl+ ions in aqueous media that damage microbial cell wall functions.[176] *N*-halamines have been added to cotton and polyester fabrics imparting antimicrobial properties resistant to laundering. Chlorine depleted over time can be restored by exposing the fabric to hypochlorite bleach.[177]

Additional antimicrobials used for the purpose of protecting materials

A number of other antimicrobials are used to protect the products to which they are added from mold, mildew, fungi, algae, and bacteria that cause staining, odors, fouling biofilms, and degradation.

The polymer polyvinylchloride (PVC) made flexible with the addition of plasticizers is subject to microbial degradation under some conditions of use. The fungicide oxybisphenoxarsine (OBPA) has a long history of use in flexible PVC but is being replaced with alternatives because of its extreme toxicity.

Isothiazolones are also used to control microbial growth in water-containing solutions, adhesives, coatings, and some personal care products. They include benzisothiazolin-3-one (BIT), Kathon 886 (CIT/MIT mixture), methylchlorothiazolinone (CIT, CMIT), and methylisothiazolinone (MIT).

These may be present in health care furnishings for purposes of protecting the material out of which the product is made. From a life cycle perspective, worker exposures to these toxic compounds are likely to be considerably more extensive than exposures from consumer products. Prolonged release of isothiazolones from water-based paint has been documented.[178] Isothiazolones can cause contact dermatitis and at least one, BIT, can cause occupational asthma. They are highly toxic to aquatic organisms but degrade fairly rapidly to less toxic byproducts within hours to days.[179]

A subgroup of organosilanes with quaternary ammonium compounds (see above) are EPA-registered bacteriostatic, algaestatic, and fungistatic compounds. Trimethoxysilyl quat- and trihydroxysilyl quat-containing products are currently used as a preservative treatment for materials such as those used in human clothing and bedding, carpets and upholstery. The trimethoxysilyl quats are used as surface treatments in household areas and bathroom areas. These products are also used in the manufacturing of paints, coatings, and concrete. The EPA has "concluded that there are no endpoints of concern for repeated oral or dermal exposure to the trimethoxysilyl quats. This conclusion is based on low toxicity observed in acute, sub-chronic and developmental studies conducted with the trimethoxysilyl quat compounds. The risk from inhalation exposure has not been characterized and an additional study designed to assess inhalation toxicity over time may be needed. In addition, severe toxicity has been observed with regard to skin and eye irritation."[180]

An extensive review of antimicrobials used solely for material and product protection is beyond the scope of this paper. However, they deserve careful evaluation and public disclosure of hazardous properties and the potential for worker, consumer, and environmental exposures.

Discussion

Healthcare-associated infections have always been a formidable challenge in hospitals and always will be. An active commitment to infection prevention, surveillance, and control must remain an essential component of health services. HAIs prolong length of stay, result in considerable morbidity and mortality, and increase costs to individuals, families, and communities. Moreover, under provisions of the Affordable Care Act, preventable readmissions to a hospital result in a financial penalty in reimbursement for all Medicare patients at that institution. HAIs that result in readmission, including MRSA and *C. difficile*, will soon be considered "preventable" and hospitals will be penalized. Consumer Reports now ranks hospitals based on HAIs, readmissions, complications, and other adverse events, making these data publicly available.[181] Thus, hospitals have financial and public relations incentives as well as ethical obligations to reduce HAIs to the extent possible.

Among determinants of the incidence of HAIs:

- Medical advances have led to many new drugs, devices, and procedures that have generated new challenges to infection control.
- An increasing number of individuals are unusually susceptible to infection.
- Greater reliance on drug therapy has sometimes displaced attention and competence away from preventive approaches.
- Antibiotic resistance has emerged rapidly in response to a general overuse and abuse of antimicrobial agents not only in treating people but also in animal agriculture. Antibiotic stewardship is an unfulfilled community-wide responsibility.
- Differences between healthcare-acquired and community-acquired infection have blurred with closer interactions among hospital- and community-based services.
- Rapid turnover in patient populations puts pressure on environmental health services and infection control personnel to properly clean and disinfect equipment and rooms.

With increased regulatory oversight, significant financial consequences, more consumer choices, and

evolving challenges in surveillance and control, hospital administrators and heath care personnel continue to look for new opportunities that will add to comprehensive, integrated efforts to reduce the incidence of HAIs.

Elements of comprehensive systems-based infection control programs include:

- Building design with evidence-based arrangements of patient rooms, procedure suites, workstations, ventilation, and other features to reduce the risk of HAIs and their spread.
- Effective, adaptive infection control committee structures.
- Continuous surveillance and evaluation of infection control procedures and training with staff (re) organization as indicated in response to findings.
- Awareness of the identity of pathogens in the community as well as in the patient population.
- Effective antibiotic stewardship by clinicians and others in the community who use antibiotics.
- Hand hygiene—the single most important practice to reduce the incidence of HAIs; strategic placement of equipment for routine hand hygiene practice and strategies to ensure full compliance with guidelines.
- Personal protective equipment and safe work practices.
- Appropriate decisions about patient placement.
- Appropriate cleaning and disinfection of buildings, equipment, and surfaces.
- Periodic reassessment of inherent hazards of cleaning materials with a goal of identifying least toxic products that can accomplish the required tasks.
- Adaptability of the frequency or intensity of cleaning and disinfecting, depending on specific patient and environmental circumstances.
- Administrative and staff support for prioritizing proper cleaning of equipment, surfaces, and the general environment with disinfection when appropriate.
- Bundles of interventions that are more effective than single measures implemented in isolation.

In the quest for continuous improvement and further reduction in HAIs, many hospital administrators and infection preventionists continue to ask, "What can we add to what we are already doing?" In this context, a number of health systems are considering adding products and materials with embedded antimicrobial agents or properties throughout their institutions as part of their infection control programs, hoping that they will help reduce the risk of HAIs.

For some pieces of medical equipment and medical devices, such as catheters and implants, the practice of adding antimicrobials has shown promising results. But with respect to furnishings, with rare exceptions, data supporting this growing practice are sparse or lacking altogether. Assays used to evaluate the antimicrobial efficacy of products with embedded antimicrobial agents typically do not mimic conditions of use and are unreliable as predictors of efficacy in a clinical setting (see Appendix C). Except for a pilot study of copper alloys on some high-touch surfaces in patient rooms and a study of copper-impregnated linens in a long-term care facility, no material or product with embedded antimicrobials has been evaluated and shown to reduce the risk of HAIs.

A recent meta-analysis of studies involving the use of antimicrobials on inanimate surfaces in health care facilities concluded that copper surfaces harbor fewer bacteria than non-copper surfaces but the quality of evidence of HAI reduction is very low and higher-quality study designs should be a priority.[182]

In addition to questioning the lack of evidence of the efficacy of added antimicrobials, epidemiologists, microbiologists, clinicians, infection control personnel, and environmental health scientists are increasingly concerned about their safety and potential tradeoffs associated with their use, in part based on the following:

- Laboratory studies show that antimicrobials added to materials and products can contribute to more widespread antibiotic resistance in pathogens. The clinical significance of these observations is unclear, but a legitimate concern is that the practice might actually make the problem worse. Inasmuch as antibiotic resistance is a growing and increasingly urgent problem, the value of adding antimicrobials to more and more products as a component of efforts to reduce HAIs should be carefully evaluated.
- Adding antimicrobials to furnishings can inadvertently create a false sense of security, resulting in the reduction of other proven pathogen-control measures, which should be employed routinely.
- In most cases, product manufacturers, infection

preventionists, and environmental services personnel simply do not know the extent to which added antimicrobials reduce microbial load under conditions of use, degrade over time with cleaning and disinfection, and how protection differs from one product to another. In most cases, the effect on incidence of HAIs is completely unknown.

- Sick patients, staff, and visitors enter the hospital with pathogens and leave a microbial footprint influenced by where they have been, establishing a dynamic microbial ecology of the building and rooms within it. Some of these people have received antibiotics or carry pathogens exposed to antibiotics in the community, for example through agricultural animal production. They may carry antimicrobial-resistant pathogens into the health care environment.

- The University of Chicago's Hospital Microbiome Project is an attempt to study the evolution of microbial communities in a newly opened hospital following introduction of patients and hospital staff.[183] The aim is to determine the influence of human population demographics, how the demographic interfaces with a space, the building materials used to create that space, microbial community succession, and rate of colonization by potential pathogens. Adding antimicrobials to more and more products in a hospital will surely further alter the microbial ecology of entire sections of a building. It is possible that antimicrobial reduction of non-pathogens on some surfaces will simply create space for more pathogenic or antibiotic-resistant organisms. We simply do not know if there is a beneficial "microbiome" in a hospital. Rather, current efforts appear to be based on an unproven assumption that any intervention resulting in a generally reduced microbial load on products and materials will help reduce HAIs.

- Environmental lifecycle safety concerns associated with manufacture, use, and disposal of antimicrobial additives in furnishings and building materials need careful consideration. Releases into the indoor and outdoor environments can result in exposures to humans and wildlife with unanticipated consequences. We have a long history of failure to anticipate these adverse impacts with other products—e.g., toxic flame retardants without demonstrated efficacy yet with widespread use in consumer products and building materials, resulting in nearly ubiquitous human and wildlife exposures and adverse health effects discovered years later—and then needing to respond after irreparable damage is done.

Conclusion

Reduction of HAIs will always be an ongoing challenge requiring comprehensive, multi-factorial interventions for prevention and control. There may be a role in an integrated program for antimicrobials added to increasing numbers of furnishings and building materials but that role is undefined and unsubstantiated.

A 2008 report from the Association for Professionals in Infection Control and Epidemiology predicted that hospitals would increase purchases of products containing antimicrobials. They are increasingly marketed as a way to reduce microbial loads on environmental surfaces with the underlying implication that using them can help reduce the risk of HAIs. Although some clearly reduce the microbial load on textiles and other environmental surfaces in laboratory settings, they have rarely been evaluated in well-designed studies for their effectiveness in clinical settings and for their contribution to reducing HAIs.

Antimicrobials in hospital furnishings may ultimately prove to be efficacious in reducing HAIs, but benefits and risks associated with their use are largely unknown. Benefits, if they exist, could presumably be measured as a reduced incidence of HAIs. Risks include increased antibiotic resistance, engendering a false sense of security with reduced attention to cleaning and disinfection, potential adverse human health and environmental impacts from exposure, and increased costs of products and materials.

Benefits at point of use, lifecycle risks, tradeoffs, and financial implications of adding antimicrobials to products in hospitals need evaluation through a well-designed research agenda that will help product designers, purchasers, infection preventionists, and environmental services personnel make more informed decisions. Until results from that research become available, design and purchasing decisions will be based mostly on hope and unverified assumptions rather than objective data. Hope and assumptions are not a sufficient rationale. Demonstrated efficacy with reduction in HAIs as part of a comprehensive infection control program and life-cycle safety evaluations are essential.

Recommendations

Inasmuch as benefits, risks, tradeoffs, and cost implications of adding antimicrobials to furnishings are active areas of research, the following recommendations are based on a current evaluation of the state of the science with the expectation that more objective data will aid in making informed design and purchasing decisions.

For health care

These recommendations are offered as a complement to comprehensive integrated infection surveillance and control programs.

- Do not specify antimicrobials in furnishings unless they have undergone EPA evaluation and registration under FIFRA and have been shown to help reduce HAIs in a clinical setting as part of an integrated infection control program.
- Ask suppliers to disclose any antimicrobials added to materials and products, even if they are used for the purpose of material preservation, the control of odor, or some other aesthetic reason.
- Take the lead or collaborate in the design and execution of a research agenda intended to address data gaps related to efficacy and risks associated with adding antimicrobials to furnishings.
- Examine antibiotic stewardship programs in your institution for opportunities to reduce the risk of generating antimicrobial resistance.
- Examine antibiotic stewardship programs in your community for opportunities to reduce the risk of generating antimicrobial resistance, including in animal agriculture. Help make the case that antibiotic stewardship to address the growing problem of antimicrobial resistance is a community-wide responsibility.

For furnishings manufacturers

- Do not make antimicrobials the standard option for any products, with the exception of antimicrobials that are used solely for product protection. Antimicrobials should be a "must select" option in order to make the decision clear, as well as to track the demand for products containing antimicrobials.
- Use only antimicrobials that have undergone EPA evaluation and registration under FIFRA and have been shown to reduce the risk of HAIs in a clinical setting unless using them is in the context of a research program to examine their efficacy.
- Take the lead or collaborate in the design or execution of a research agenda intended to fill data gaps related to efficacy and risks associated with adding antimicrobials to furnishings.
- Require full toxicity testing, studies of potential leaching, and evaluations of potential human or environmental exposure to any antimicrobials used in products.
- Align sales and marketing claims with EPA FIFRA labeling requirements.
- Investigate and make publicly available information about the presence of all antimicrobials in products, including antimicrobials that are exempt from FIFRA registration because of the Treated Articles Exemption.

For manufacturers of antimicrobials

- Conduct full toxicity testing, including environmental toxicity, fate, and transport, as well as life-cycle assessment of any antimicrobials, including antimicrobials used for purposes of preserving the product, and make results publicly available.
- Collaborate to develop clinically relevant testing methods to determine efficacy in the clinical setting.
- Align sales and marketing claims with EPA FIFRA labeling requirements.
- Commit to transparency in toxicity and efficacy testing for all antimicrobials.

For the research community

- Prioritize research to determine efficacy, risks throughout the life-cycle, tradeoffs, and cost implications of the use of antimicrobials in furnishings in clinical settings.
- Research hazard profiles and potential human and environmental exposures to antimicrobials used for purposes of preserving the product.
- Research whether the addition of antimicrobials in products changes the microbial ecology (microbiome) of a building or spaces within a building and whether those changes have clinical or public health significance.

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Appendices

Appendix A

Methods For Evaluating The Thoroughness Of Cleaning And Disinfection

Whenever the thoroughness of cleaning and disinfecting practices are being evaluated, observers must keep in mind the Hawthorne effect. Also known as the observer effect, it refers to a modification of a practice when an individual is aware of being observed. Random, unannounced, unobserved evaluations of the thoroughness of cleaning and disinfecting practices can help eliminate this effect and contribute to infection control program improvements.

Direct observation:
Covert visual monitoring of actual cleaning practices can provide assessment of individual staff performance and compliance with guidelines. This approach is mainly useful for research purposes, education, and certification but impractical for routine monitoring.

Swab cultures of surfaces:
Swab cultures taken from environmental surfaces according to established protocols can identify numbers and kinds of organisms recovered. One proposal concludes that more than five aerobic colony forming units (CFUs)/cm^2 on high touch surfaces after terminal cleaning is evidence of an inadequate cleaning and disinfecting process.[1] This method is useful for research into the effectiveness of various cleaning practices, but costs, delays in obtaining results, and the need for information about pre-cleaning conditions limits its utility for routine monitoring. It can, however, be helpful in tracing the origins of an identified cluster of HAIs.

Agar-coated glass slides:
Agar-coated glass slides pressed onto the surface being evaluated and then incubated can quantify the number of aerobic CFUs/cm^2. This method is useful for periodic monitoring of cleaning efficacy but shares some of the same limitations as swab cultures.

Fluorescent markers:
Fluorescent powders, lotions, or gels—poorly visible or invisible in ambient light but fluorescent in UV light—applied before cleaning can be used as markers to evaluate the thoroughness of surface cleaning. Using this method, documentation of opportunities to improve cleaning practices has led to improvements, reduction of surface bioburden of pathogens, and decreased MRSA and VRE transmission.[2] However, the method only evaluates cleaning directly and not disinfecting.

Adenosine triphosphate bioluminescence:
Adenosine triphosphate (ATP) bioluminescence technology detects the presence of organic debris, including viable and nonviable bioburden, on surfaces. Although this method is relatively easy to use, its modest specificity for various important hospital pathogens and high sensitivity to non-viable organic material limits its value for routine monitoring.[3]

Appendix B

CDC Guidelines For Hand Hygiene: Safety And Efficacy Of Agents

The pathway of transmission of pathogens on hands from one person to another:

- Organisms on a person's skin, or that have been shed on objects close to the person, are transferred to the hands of someone else. If that is a health care worker or a patient visitor, a potential chain of transmission is initiated.
- These organisms must then be capable of surviving for at least a short period of time on the hands of personnel.
- Handwashing or hand antisepsis by the worker must be inadequate or omitted entirely, or the agent used for hand hygiene must be inappropriate.
- Finally, the contaminated hands of the caregiver or visitor must come in direct contact with another patient or with an inanimate object that will come into direct contact with the patient.

Products intended for use as health care worker hand washes are evaluated for efficacy using a standardized method.

Current CDC definitions of hand hygiene products

- *Alcohol-based hand rub.* An alcohol-containing preparation for application to the hands intended to reduce the number of viable microorganisms. In the United States, these preparations usually contain 60%–95% ethanol or isopropanol.
- *Antimicrobial soap.* Soap (i.e., detergent) containing an antiseptic agent.
- *Antiseptic agent.* Antimicrobial substances applied to the skin to reduce the number of microbial flora. Examples include alcohols, chlorhexidine, chlorine, hexachlorophene, iodine, chloroxylenol (PCMX), quaternary ammonium compounds, and triclosan.
- *Antiseptic handwash.* Washing hands with water and soap or other detergents containing an antiseptic agent.
- *Antiseptic hand rub.* Applying an antiseptic hand-rub product to all surfaces of the hands to reduce the number of microorganisms present.
- *Detergent.* Detergents (i.e., surfactants) are compounds that possess a cleaning action. They are composed of both hydrophilic and lipophilic parts and can be divided into four groups: anionic, cationic, amphoteric, and nonionic detergents.
- *Hand antisepsis.* Refers to either antiseptic handwash or antiseptic hand rub.
- *Hand hygiene.* A general term that applies to handwashing, antiseptic handwash, antiseptic hand rub, or surgical hand antisepsis.
- *Handwashing.* Washing hands with plain (i.e., non-antimicrobial) soap and water.

The CDC produced the most recent guidelines for hand hygiene in the health care setting in 2002. [4] [5] These guidelines review the efficacy of plain soap, alcohols, chlorhexidine, hexachlorophene, iodine-containing compounds, chloroxylenol, quaternary ammonium compounds, and triclosan.

The Food and Drug Administration (FDA) is responsible for evaluating the safety and effectiveness of over-the-counter antiseptic drug products.

FDA classification scheme:

I. Conditions under which antimicrobial products are generally recognized as safe and effective and are not misbranded.
II. Conditions under which antimicrobial products are not generally recognized as safe and effective or are misbranded.

III. Conditions for which the available data are insufficient to permit final classification at this time.

Current classification of agents according to this scheme, according to the 1994 tentative final monograph or proposed rule (the 1994 TFM), which has been revised and was open for public comment until October 2015:

- Alcohol, 60-85% (I)
- Povidone-iodine, 5-10% (I)
- Hexachlorophene (II)
- Chloroxylenol (PCMX) (III)
- Quaternary ammonium compounds
  - Benzalkonium chloride (III)
  - Benzethonium chloride (III)
- Triclosan, <1% (III)
- Triclocarban (III)

According to the FDA, when hands are not visibly dirty, soiled, or contaminated, alcohol-based products are more effective for standard handwashing or hand antisepsis by health care workers than non-antimicrobial soap or antimicrobial soap and water. When hands are visibly contaminated, they should be cleaned with soap and water before using alcohol-based products.

A comparison of the classification of OTC health care personnel hand wash and surgical hand scrub antiseptic ingredients in the proposed rule and in the 1994 TFM is as follows:

Active ingredient	**1994 TFM**	**Proposed rule**
Alcohol, 60-90%	I	IIISE
Hexylresorcinol	IIIE	IIISE
Iodine cmplx (ammonium ether sulfate & polyoxyethelene sorbitan	IIIE	IIISE
monolaurate)	IIIE	IIISE
Iodine cmplx (phosphate ester of alkylaryloxy polyethylene glycol)	IIIE	IIISE
Isopropyl alcohol, 70-91.3%	IIIE	IIISE
Nonylphenoxypoly (ethyleneoxy) ethanoliodine	IIIE	IIISE
Poloxamer iodine complex	I	IIISE
Povidone-iodine, 5-10%	IIIE	IIISE
Secondary amyltricresols	IIIE	IIISE
Triclocarban	IIIE	IIISE
Undecoylium chloride iodine complex		

"E" refers to effectiveness.

"S" refers to safety.

"I" denotes sufficient data.

"III" denotes need for more data.

No changes in classification are proposed for:

- Benzalkonium chloride (IIISE)
- Benzethonium chloride (IIISE)
- Chloroxylenol (IIISE)
- Cloflucarban (IIISE for health care personnel hand wash, II for surgical hand scrub)
- Fluorosalen (II—unsafe, ineffective, or both)
- Hexachlorophene (II)
- Methylbenzethonium chloride (IIISE)
- Phenol (less than 1.5 percent) (IIISE)
- Phenol (greater than 1.5 percent (II)
- Sodium oxychlorosene (IIISE)
- Tribromsalan (II)
- Triclosan (IIISE)

Appendix C

Test Methods

The antimicrobial efficacy of textiles and other materials that may harbor microbes is typically evaluated in a laboratory, using established protocols in which a small piece of the antimicrobial-impregnated material or coated surface is incubated in a test tube, flask, or petri dish containing bacterial cultures and measuring colony count reduction after a prescribed period of time.[6] [7] [8] Rarely studies are conducted in a clinical setting to document reduced microbial loading, persistence of antimicrobial activity with use and cleaning, disinfecting, or laundering in that setting.[9]

The most commonly used test method for evaluating antimicrobial activity of a solid surface material is the Japanese Industry Standard JIS Z 2801, also published as ISO22196.[10]

Commonly used quantitative test protocols for antimicrobially-treated textiles are AATCC Test Method (TM) 100 (American Association of Textile Chemists and Colorists), JIS L 1902 (Japanese Industrial Standard), and ISO 20743 (International Standards Organization). These methods inoculate and then recover microbes, with the result reported as a percent or $\log_{10}$ reduction in contamination between either an initial inoculation level of bacteria or against an untreated control. Antimicrobial textiles can also be subject to tests after repeated laundering to evaluate the extent to which they maintain antimicrobial properties.

Method	Title	Summary	Strengths	Weaknesses	Realistic Model System?
AATCC 147	Antibacterial Activity Assessment of Textile Materials: Parallel Streak Method	Thin strips of test fabrics are laid onto petri dishes that have been inoculated with test microorganisms. In this test, bacterial test organisms, such as Staphylococcus aureus and Klebsiella pneumoniae, are streaked onto agar plates in a series of five streaks. Treated and untreated fabric samples are placed over the streaks, and the plates are incubated. Zones of growth inhibition are qualitatively analyzed visually after incubation and the treated materials	Relatively inexpensive and quick. Fabrics must normally have considerable activity levels to demonstrate "zones of inhibition."	Non-quantitative method makes comparisons with other products or technologies difficult. The method cannot differentiate "kill" from growth inhibition.	Not realistic. The microbial inoculum generally only contacts the surface of the fabric, and the surface of the agar is wetter and more nutritive for a longer period of time than would be expected in real situations.

		are compared to the untreated control materials to draw conclusions about the degree of antibacterial activity observed. This method is generally used to substantiate antibacterial properties of treated fabric for non-public health related claims. No regulated limits currently exist for general antibacterial claims made using this method.			
AATCC 100	Assessment of Antibacterial Finishes on Textile Materials	Test and control fabrics are effectively saturated, side-by-side, with a nutritive but dilute suspension of microorganisms. Microbial concentrations on the fabrics are enumerated at "time zero" and also after the contact period has elapsed. Differences between test and control fabrics are used as the basis for antimicrobial activity level (microbial reduction or growth inhibition) determinations. •The test microorganism is grown in liquid culture. •The concentration of the test microorganism is standardized. •The microbial culture is diluted in a sterile nutritive solution.	Quantitative method that is well designed in terms of technicalities related to the testing of antimicrobial agents (includes antimicrobial agent neutralization controls, etc).	Only a single replicate of the test is normally performed. The method has vague success criteria, so that the company sponsoring the study can decide whether the material qualifies as having antimicrobial properties (the method states that "the criteria for success must be decided by the interested parties"). Although organisms used in quantitative tests can vary, most methods call for testing against at least one Gram-negative (e.g., Escherichia coli or Klebsiella pneumoniae) and one Gram-positive (e.g. Staphylococcus aureus) organism.	Very realistic with respect to prevention of microbial growth or kill of microorganisms in wet fabrics, and possibly even a conservative model. Unrealistic in that fabrics are kept wet (most antimicrobial agents work best in the presence of liquid) for the full contact period, which is often a full 24 hours. Thus, reductions of dried microbial inocula on fabrics in "real-life" may not be as dramatic as results might suggest.

		•Control and test fabric swatches are inoculated with microorganisms. •The inoculation is performed such that the microbial suspension touches only the fabric. •Bacteria levels on both control and test fabrics are determined at "time zero" by elution in a large volume of neutralizing broth, followed by dilution and plating. •A control is run to verify that the neutralization/ elution method effectively neutralizes the antimicrobial agent in the fabric. •Additional inoculated control and test fabrics are allowed to incubate, undisturbed in sealed jars, for 24 hours. •After incubation, microbial concentrations are determined. •Reduction of microorganisms relative to initial concentrations and the control fabric is calculated.		Another often mentioned limitation of these tests centers on their stipulated parameters of temperature, relative humidity, and method of application of the microbial load, which do not reflect conditions typical of the clinical environment. Their performance in environmental conditions of use may vary considerably. Yet, products made of these materials are usually marketed as having antimicrobial properties based on the results of these laboratory tests	

ASTM E2149	Standard Test Method for Determining the Antimicrobial Activity of Immobilized Antimicrobial Agents Under Dynamic Contact Conditions	Test and control fabrics are placed individually into 50 mL of a non-nutritive suspension of test microorganisms and shaken vigorously for the contact period (usually 24 hours). Microbial concentrations in solution are determined at "time zero" and after the contact period. Microbial reductions are calculated.	Quantitative method.	Only a single replicate of the test is normally performed. No clear standards are set for "pass" or "fail" by the method.	Not realistic in any sense. Fabrics are submerged in a great relative volume of liquid and shaken in a non-nutritive suspension for long periods of time. The method states that active ingredient should be "non-leaching" but does not include sufficiently sensitive methods for testing for leaching of the antimicrobial into the test solution.
JIS L 1902 (Quantitative Aspect)	Testing for Antibacterial Activity and Efficacy on Textile Products	Three replicates of test and control fabrics are inoculated, side-by-side, with a slightly nutritive and dilute suspension of microorganisms. Microbial concentrations on the fabrics are enumerated at “time zero” and also after the contact period has elapsed. Differences between test and control fabrics are used as the basis for antimicrobial activity level (microbial reduction or growth inhibition) determinations.	Quantitative method that is well designed in terms of technicalities related to the testing of antimicrobial agents (includes antimicrobial agent neutralization controls, etc). Three replicates are required.	The microbial inoculum used for this method is much less nutritive than that used for AATCC 100, making the method less conservative.	Fairly realistic with respect to kill of microorganisms in wet fabrics, but may not be representative of activity in dirty fabrics. Unrealistic in that fabrics are kept wet (most antimicrobial agents work best in the presence of liquid) for the full contact period, which is often a full 24 hours. Thus, reductions of dried microbial inocula on fabrics in “real-life” may not be as dramatic as results might suggest.

JIS Z 2801, ISO22196	Japanese Industry Standard JIS Z 2801; also used for assessing antimicrobial activity of plastics and other solid materials	•The test microorganism is prepared, usually by growth in a liquid culture medium. •The suspension of test microorganism is standardized by dilution in a nutritive broth, affording microorganisms the potential to grow during the test. •Control and test surfaces are inoculated with microorganisms, in triplicate, and then the microbial inoculum is covered with a thin, sterile film. Covering the inoculum spreads it, prevents it from evaporating, and ensures close contact with the antimicrobial surface. •Microbial concentrations are determined at "time zero" by elution followed by dilution and plating. •A control is run to verify that the neutralization/elution method effectively neutralizes the antimicrobial agent in the antimicrobial surface being tested. •Inoculated, covered control and antimicrobial test surfaces are allowed to incubate	The method is quantitative and tends to be reproducible, provided the inoculum does not spill off of the target area after being covered with the thin film. The method tests for both bacteriostatic and bactericidal properties. Microbial concentrations are standardized, and bacteria are provided with nutrients during the incubation period, which provides them with ample opportunity to grow if surfaces aren't sufficiently antimicrobial. This is in contrast to certain antimicrobial tests, where microbes are "incubated" in non-nutritive suspensions, which itself may be stressful over long periods.. The method stipulates triplicate experimentation.	The JIS Z 2801 method is not necessarily representative of actual surface contamination events, since a relatively dilute liquid microbial inoculum is spread over a considerable surface area, and then is kept wet (usually for a period of 24 hours). Most of the time, microbial contaminants dry quickly onto surfaces. This limits the time that an aqueous medium is available to facilitate interaction between the antimicrobial surface and microorganisms . This means that JIS Z 2801 is a "best-case" sort of test for many products.	Fairly realistic with respect to kill of microorganisms in wet fabrics, but may not be representative of activity in dirty fabrics. Unrealistic in that fabrics are kept wet (most antimicrobial agents work best in the presence of liquid) for the full contact period, which is often a full 24 hours. Thus, reductions of dried microbial inocula on fabrics in "real-life" may not be as dramatic as results might suggest.

		undisturbed in a humid environment for 24 hours. •After incubation, microbial concentrations on are determined. Reduction of microorganisms relative to initial concentrations and the control surface is calculated.	The method includes a “pass/fail” criterion for the calculated levels of antimicrobial activity observed in test samples, making determinations of antimicrobial activity less discretionary.		

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List of Acronyms

AHRQ	Agency for Healthcare Research and Quality
BPR	Biocidal Product Regulation
CDC	Centers for Disease Control and Prevention
CRE	Carbapenem-resistant enterobacteriaceae
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAIs	Healthcare-Associated Infections
HPV	Hydrogen peroxide vapor
ICU	Intensive care unit
IHI	The Institute for Healthcare Improvement
MDROs	Multidrug-resistant organisms
MERS	Middle East respiratory syndrome
MRSA	Methicillin-resistant *Staphylococcus aureus*
NIOSH	Healthcare Working Group of the National Institute for Occupational Safety and Health
NORA	National Occupational Research Agenda Working Group
OTC	Division of Over-the-Counter Drug Products (Over the counter)
PVC	Polyvinylchloride
RCTs	Randomized controlled clinical trials
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
ROS	Reactive oxygen species
SARS	Severe acute respiratory syndrome
SENIC	Study on the Efficacy of Nosocomial Infection Control
SHEA	Society for Healthcare Epidemiology of America
TFM	Tentative Final Monograph for Healthcare Antiseptic Drug Products
UVGI	Ultraviolet germicidal irradiation
VRE	Vancomycin resistant enterococci

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