Novel Antimicrobial Surface Coatings And The Potential For Reduced Fomite Transmission Of SARS And Other Pathogens
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Abstract

Surface bio-contamination is a problem that contributes to outbreaks of community-acquired and nosocomial infection through episodic fomite transmission of disease and through persistent fomitic reservoirs. The extent to which fomitic reservoirs contribute to the overall extent of nosocomial infection is unknown, but fomites are known to play some role in the transmission of many diseases, including SARS.

Faster surface die-off of pathogens on a surface can significantly reduce the amount of time that a fomitic reservoir is capable of transmitting disease, and can also reduce the average surface population of pathogens available for transmission to a susceptible host.

Effective routine chemical disinfection is difficult because strong chemical solutions must be applied correctly and left in contact with surfaces for prolonged periods of time. Many materials are not amenable to such treatments, and many clinical environments do not accommodate them easily.

Exotic metal-containing antimicrobial surface materials provide broad-spectrum antimicrobial activity through the controlled release of metal ions. Zeolites are porous crystal-structured aluminosilicate particles that can be manufactured with metal ions within their pores and are capable of releasing ions at a controlled rate for many years, while withstanding the heat and pressures typical of manufacturing processes. A readily-available formulation of silver-zinc zeolite (AgION Technologies, Inc, Wakefield, MA) has proven effective against a variety of pathogens in a variety of environments, and has been incorporated in a number of different materials of potential use in healthcare.

An initial experimental study of SARS inactivation by silver zeolite antimicrobial powder has shown inactivation in bulk suspension within as little as two hours. Real-world silver zeolite surfaces routinely achieve surface silver ion concentrations much higher than those achieved in bulk suspension, thus likely can reduce the survival time of SARS on treated surfaces to two hours or less.

Introduction

In 1999 and 2000, the United States Department of Health and Human Services and the Office of Emergency Preparedness designated special funds for a project to enhance hospital and emergency care facility readiness by identifying needed improvements in surge capacity, designed-in safety, and special capabilities. In the first phase of the project ("Federal Project ER One") a series of expert task forces were convened for a year-long effort to assess the shortcomings of current approaches to hospital readiness and to define guiding principles and potential solutions. The results of that “Phase I” effort have been published in a book and CD-ROM, and are also available on the ER One website. 1 In 2004, initial construction funds for
Project ER One were appropriated as part of the Health and Human Services omnibus bill signed by President Bush.

One of the most important problems identified during phase I of the ER One project was that of facility surface bio-contamination and decontamination. One of the most interesting emerging solutions identified during the project was that of novel antimicrobial surface coatings with the potential to reduce or eliminate many of the problems associated with bio-contamination.

**Surface contamination**

Facility bio-contamination not only presents a health risk for those within the facility, but also has the potential to render a facility unusable for some period of time. For example, the Brentwood postal facility in Washington, DC was removed from service for several years after a small quantity of anthrax was sent through the mail and facility contamination occurred.\(^2\)

If an outbreak is believed to be related to facility contamination, the social and financial impact can persist long after decontamination is complete. A 1989 outbreak of Ebola-Reston at the Reston Primate facility near Washington DC led to the death of many monkeys, but no humans.\(^3\) The facility was vacated and underwent extensive decontamination procedures.\(^4\)\(^5\) Despite assurances that no active virus remained in the structure, the landlord was never able to sell the building nor to find another tenant. The building was demolished in 1995, after remaining vacant for six years.

When facility contamination is recognized, it often is in the context of clusters of disease recognized as outbreaks of community-acquired or nosocomial infection, as when an outbreak of respiratory disease leads to recognition of legionella growing within cooling towers and other moist locations.\(^6\) Clusters of neurologic symptoms due to facility contamination with stachybotrys and other mycotoxin-producing molds have led to the abandonment of many buildings,\(^7\) but most healthcare facility contamination events are not so dramatic. In a healthcare facility, occult contamination events are common, as endemic, epidemic, or emerging illness frequently enters a healthcare facility and goes unrecognized for many hours or days.\(^8\) Bio-contamination may be spread widely by the time the problem is identified.

**Nosocomial infection**

Although it is known that surface contamination can play a role in nosocomial infection, the extent to which contaminated surfaces contribute to the overall problem is uncertain.

Deaths due to nosocomial infections are estimated at 80,000 per year\(^9,10\) at an economic cost of more than $5 billion annually.\(^11\) Hospital-acquired bloodstream infections alone account for about 1% of all deaths due to disease, ranking it the eighth leading cause of death in the United States.\(^12\) A particular risk exists among patients in the intensive care unit (ICU) where nosocomial infections can be over 5 times more prevalent than among non-ICU patients.\(^13\) Discussion of nosocomial infection tends to focus on the problem of antibiotic-resistant bacteria, but in an acute-care hospital setting, nosocomial viral infections may also cause serious problems. Viruses may account for 30% of nosocomial infections in some pediatric settings.\(^14\) For a postoperative transplant patient, even a common cold can prove fatal.
Transmission of nosocomial infection can be airborne or it may occur through physical contact. For some types of infection, such as tuberculosis, the primary transmission mechanism is airborne, while for others, such as nosocomial bloodstream infection, the primary mode of transmission is through physical contact. Physical transmission can be direct (person-to-person contact) or indirect (person-to-object-to-person). The intermediary object involved in indirect transmission is termed a fomite, from the Latin word fomes, meaning “tinder.” A fomite is “an inanimate object or substance that is capable of transmitting infectious organisms from one individual to another.” Fomites can be macroscopic surfaces, or they can be loose particles such as grains of dust, fibers, dirt, hair, and skin cells, which may at times be suspended in the air but most often settle on macroscopic surfaces. Fomitic surfaces may be passive reservoirs (receiving a load of contaminants that gradually dies away over time) or active participants, supporting the growth and spread of disease-inducing organisms.

Direct physical contact between healthcare workers occurs only occasionally, most often through handshaking, but inanimate objects are frequently passed from person to person, and healthcare workers often come into contact with common fomitic surfaces within moments of another person’s contact with the same surface. Direct physical contact between healthcare workers and patients occurs more frequently, and inanimate objects may also be intermediaries in the transmission of contamination between patients and staff. A strong emphasis is placed on the importance of handwashing before and after each episode of contact between staff and patients, yet fomitic objects such as stethoscopes rarely receive the same treatment, and relatively little attention has been paid to other common contact surfaces such as doorknobs, wallplates, faucets, countertops, bedrails, carts, telephones, pens, and clipboards.

Bio-contamination is a constant risk in a healthcare environment. The patient whose hands are shown in Figure 1 shook hands with several staff members before being diagnosed with syphilis, which can be communicated through the lesions shown. He also touched an unknown number of doorknobs, wallplates, bedrails, and other surfaces.
Traditional approaches to practical infection control have focused on erecting respiratory barriers and on reducing direct person-to-person transmission. However, the continuing epidemic of nosocomial infections is evidence enough that face masks and hand-washing campaigns alone are not sufficient to cure the problem.

**Pathogens on Hospital Surfaces**

The everyday presence of pathogens on common hospital surfaces is well documented, and reducing the environmental reservoir is recognized as a positive step as part of an overall strategy to reduce nosocomial infections. Common pathogens can survive on surfaces for an extended time and can be transferred to patients. VRE has been cultured from monitor knobs, doorknobs, gowns, linens, bed rails, side tables, IV pumps, pressure cuffs, walls, floors, wall plates, and many other environmental surfaces. Dry cotton fabrics have been shown to support vancomycin resistant *Enterococci* (VRE) for up to 18 hrs and fungi for over five days. VRE has also been found to survive on surfaces and equipment for over three days. In one study of potential fomitic surfaces in a hospital, countertops inoculated with *E. faecalis* and *E. faecium* showed survival for five and seven days, respectively. In the same study bed rails supported both species for 24 hours, telephones and fingers (gloved or not) for 60 minutes, and stethoscope diaphragms for 30 minutes. Pseudorabies virus remains infectious on steel surface for 7 days.
Common coronaviruses, known to be transmissible by fomites, are able to survive on ordinary environmental surfaces for up to 3 hours.\textsuperscript{29, 30} Chlamydia can survive on surfaces for a similar period.\textsuperscript{31}

A wide variety of surfaces can become contaminated under ordinary clinical conditions. Within 7 days of the onset of a zoster eruption in a hospitalized patient, varicella virus was detected on all tested room surfaces, including the back of a chair, the door handle, the table and the air conditioner filter.\textsuperscript{32} Parainfluenza and herpes simplex both survive on untreated toothbrushes for at least 24 hours.\textsuperscript{33} Herpes simplex remains infectious for at least 8 hours on a moist applanation tonometer.\textsuperscript{34} Recent evidence suggests that hospital environments are particularly likely to serve as a reservoir for Methicillin-resistant staphylococcus aureus (MRSA) and Vancomycin-resistant enterococcus (VRE) as compared with gram-negative bacteria.\textsuperscript{35}

A team from the Centers for Disease Control (CDC) investigated the role of environmental transmission of disease at two hospitals that had contained SARS patients and found a high proportion of surface swabs positive for SARS viral RNA. Contamination was found on many surfaces in patient rooms as well as in nearby nursing stations and other parts of the hospital. Contaminated surfaces included computer "mice" at the nursing station and the handrail of the public elevator.\textsuperscript{36}

In the 1980s a National Institutes of Health campaign to promote hand washing used a stuffed teddy bear (“T. Bear") as a handwashing spokesperson and as a promotional item. Ironically, a prospective study of 39 sterilized T. Bears released into a pediatric ward found that 100% were colonized with bacteria, fungi, or both within 1 week. Nosocomial organisms cultured from the bears included Staphylococcus epidermidis, Staphylococcus aureus, Alpha Streptococci, Corynebacterium acnes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Micrococcus sp, Bacillus sp, and species of Candida, Cryptococcus, Trichosporon, Aspergillus and others.\textsuperscript{37}

Fomitic surfaces that are transported between hospital rooms are of particular concern, and have been implicated in nosocomial outbreaks. In one study, significant bacterial contamination was found on 92.9% of 42 writing tools taken from 42 doctors\textsuperscript{38}. Fifteen different genera and species were isolated including methicillin-resistant staphylococci. French\textsuperscript{39} reports a similar experience in which 36 pens were tested from wards experiencing outbreaks of MRSA, VRE and Multiple drug resistant (MDR) \textit{Klebsiella pneumoniae}. From the wards affected by MRSA, 25% of the pens possessed the outbreak strain. From the wards affected by VRE, 17% of the pens were colonized with VRE. None of the pens from the MDR Klebsiella ward showed contamination by the MDR strain, which the authors attribute to a greater susceptibility of Klebsiella to drying than the gram-positive organisms. However, the authors also note from other references that in some cases “…\textit{Klebsiellas} can survive quite well on surfaces.” When 55 stethoscopes and 42 otoscopes used by physicians in community clinics were swabbed for culture, 100% of stethoscopes and 90% of otoscopes were colonized or contaminated by a variety of organisms, including several contaminated with methicillin-resistant staphylococcus aureus.\textsuperscript{18}
Fomite transmission of illness

Many examples exist of recognized fomite-related nosocomial illness. The occurrence of VRE is strongly associated with patient placement in a room where a prior occupant has had VRE, even after extensive cleaning.\(^4^0\) An outbreak of Carbapenem-resistant Acinetobacter in the UK was traced to environmental surfaces, including fabric curtains, that served as a fomitic reservoir.\(^4^1\) Fomite transmission via contaminated beer glasses was implicated in a hepatitis A outbreak among visitors to a pub.\(^4^2\) Fomite transmission via contamination of a radiant warmer was blamed for the transmission of DNA-identical herpes in a neonatal nursery, resulting in the death of several patients.\(^4^3\) Fomites have been identified as a likely source for the transmission of chlamydial infection to the eye, especially under humid conditions, when chlamydia can survive on surfaces for 3 hours.\(^4^4\) Health care facility bio-contamination with fungi has been associated with outbreaks of rheumatoid disease.\(^4^5\)

Since the outbreak of sudden acute respiratory syndrome (SARS) in Asia and its spread to other parts of the world, additional attention has been focused on contaminated surfaces as a contributor to the problem of disease transmission. While direct person-to-person transmission via respiratory droplets accounted for most cases, and remote airborne transmission may have accounted for a few others, the Centers for Disease Control (CDC) of the United States Department of Health and Human Services (HHS) publication, “Draft Public Health Guidance for Community-Level Preparedness and Response to SARS” also cites fomite transmission and comments on the long survival time of SARS-CoV observed on inanimate surfaces.\(^4^6\)

The World Health Organization (WHO) Consensus document on the epidemiology of SARS also presents evidence implicating fomitic transmission. In some cases, victims appear to have contracted the disease after coming into contact with contaminated surfaces several days after the original source case had passed through an area. This is a credible suggestion because SARS-CoV virus can remain stable on surfaces for days under many different environmental conditions.\(^4^7\) For example:

- At low temperatures (4°C and -80°C) there is only minimal reduction in virus concentration in cell-culture supernatant. This has implications for the survival of viral reservoirs through the winter and in refrigerated food storage areas.
- The virus in cell-culture supernatant reduces by only one log after 2 days at room temperature, indicating that the virus is somewhat more stable than other known human pathogenic coronaviruses under such conditions.
- The virus is stable in ordinary feces and urine at room temperature for at least 1-2 days.
- The virus is stable for up to 4 days in stool from patients with diarrhea, probably due to a higher pH diarrheal stool compared with normal stool.
- Laboratory suspensions of SARS-CoV retain infectivity for 9 days, and dried samples retain infectivity for 6 days.\(^4^8\)
- In Canada, environmental samples from many surfaces (including walls and components of the ventilation system) tested PCR positive for SARS-CoV.
- The Chinese University in Hong Kong has demonstrated that SARS-CoV (in sterilized stool or phosphate buffered saline) survives for several days at room temperature on a variety of surfaces (Figure 2).
When all the evidence is examined, it is likely that some significant percentage of SARS cases had fomite transmission somewhere in the chain of transmission. The authors of the WHO document conclude that additional guidance is needed for effective surface decontamination methods that are “…good enough to prevent transmission of SARS-CoV and other common infections while remaining practical.”

**Fomitic reservoirs**

Although most pathogens begin to dessicate immediately after being deposited onto a surface, fomitic transmission of many agents may still occur for days to weeks. Many hours after initial surface contamination, relatively high numbers of bacteria may be transferred from an apparently dry stainless steel surface through a brief (10 second) episode of contact.

Depending on environmental conditions, pathogens may remain infectious on surfaces for weeks after the contamination event. In humid conditions, pathogens may actively colonize surfaces, transforming a passive reservoir into an active one. Furthermore, formation of biofilm by one bacterial agent can affect the survival of other pathogens on the same surface.

Hospitals by their very nature contain large numbers of sick people, many of whom carry infectious diseases that can be spread by direct or indirect contact. Hospital surfaces therefore are subject to a constant background incidence of contamination events as patients and staff move...
from place to place and come into contact with surface after surface. Chronic fomitic reservoirs arise when repeated contamination re-seeds a surface faster than the organism dies off, or when environmental conditions permit an organism to grow and propagate on the surface.

**Problems with consistent cleaning**

After a recognized bio-contamination event, intensive efforts are directed at decontamination and facility rehabilitation, but these efforts usually are limited in time and space. Where contamination is ongoing, decontamination must also be constantly ongoing if it is to be effective. Occult contamination events do not trigger aggressive efforts to clean and scrub with appropriate chemical solutions, thus if routine cleaning is not sufficient to eradicate contaminants, occult contamination may remain on surfaces indefinitely.

Many ordinary surfaces can be adequately decontaminated with routine disinfection, but many other common hospital surfaces, such as upholstery and carpets, cannot. For example, contamination with VRE persists in 16% of rooms after "standard" terminal cleaning. Some surfaces, such as curtains, can be taken away and sterilized, but this is not a part of routine cleaning in most facilities. Cracks, crevices, and inaccessible areas may also become reservoirs of disease.

Commonly-used disinfection techniques are incapable of eradicating fomite reservoirs of nosocomial pathogens such as methicillin-resistant Staphylococcus Aureus (MRSA). In fact, traditional cleaning techniques – even some using alkylamines and quaternary ammonium compounds -- may do more to spread contamination than to reduce it. At the same time, quaternary ammonium, phenols, and chlorine sanitizers are irritating to asthmatic or respiratory-impaired patients and staff.

Impractically long chemical exposure (long dwell times) may be necessary to eradicate fomite reservoirs, particularly when the bacterial load is high or the disinfecting chemical is dilute. Certain resistant viruses also require impractically long exposures for inactivation. For example, a common solvent-detergent combination inactivates many viruses within 30 minutes, but requires up to 24 hours to inactivate vaccinia.

To compound the problem, hospital locations such as the emergency department or the intensive care unit may be overloaded around-the-clock with very sick patients, rendering regular surface disinfection impractical. Where constant manual disinfection of surfaces and objects is impractical, the selection of surfaces and disinfecting residues that provide sustained intrinsic or extrinsic antimicrobial activity may help to reduce the fomitic transmission of disease.

Episodes of cross contamination can occur in a very short period of time, thus unless surface killing is complete and instantaneous, it will not prevent all episodes of cross-contamination. However, pathogen die-off need not be complete and instantaneous to reduce the transmission of infection. A reduction in clinical transmission may occur if there is a reduction in the total time during which a fomitic reservoir is active. Reduced transmission can also occur if there is a reduction in the size of the fomitic reservoir, because for many pathogens, the likelihood of clinical infection is directly related to the number of organisms to which a patient is exposed. Reducing the size of the fomitic reservoir can reduce number of
pathogens reaching a susceptible host, perhaps below the threshold needed for transmission of infection.

The size of a fomitic reservoir is determined by the balance between inoculation and die-off. Even in the absence of propagation, bacteria and viruses can survive on untreated surfaces for hours to days, therefore the surface reservoir at any given time consists of microorganisms that have been inoculated onto that surface over the previous hours to days. This reservoir may be much larger than that produced by a single contaminating event. For example, if a surface is contaminated hourly with 1000 units of pathogen, and that pathogen dies off gradually at a constant rate over 24 hours, the number of pathogens on that surface will increase to a steady state as shown in Figure 3 A. If the pathogen instead survives only 4 hours on a disinfected or otherwise treated antimicrobial surface, a lower steady state degree of contamination is reached, as shown in Figure 3 B.

![Figure 3: The effect of survival time on the accumulation of microorganisms on a conventional surface, as compared to an antimicrobial surface. Survival times are typical of experimentally determined survival times observed for common pathogenic organisms on treated and untreated surfaces.](image)

Reducing the survival time on surfaces thus reduces the size of the fomitic reservoir, a recognized objective in preventing the spread of disease.9,11,12 For a pathogen susceptible of fomitic transmission, an ongoing rate of surface inoculation, and a real-world transmission efficiency, there is some surface survival threshold above which an outbreak will result. Under some circumstances, speeding the die-off of organisms on a surface can make the difference between a sustained outbreak and a self-limited contamination event.
Exotic antimicrobial surfaces

Given the difficulty of controlling surface contamination through active cleaning, there is a significant appeal to the promise of exotic surface coatings that can self-decontaminate after a bio-contamination event – even an unrecognized one.

Exotic antimicrobial surface coatings originally were developed to inhibit the growth of organisms on chronically moist surfaces such as are found in food-service industry workplaces. Such coatings have also proven effective in preventing the development of biofilms both in industrial and in medical applications, and have been incorporated into many consumer products from air handlers and sweat-socks to water-bottles, as well as medical devices such as indwelling catheters and stainless steel orthopedic devices.

Several technologies exist that can impart antimicrobial properties to surfaces of coatings and plastics. Most release an active ingredient from the surface that interacts with microorganisms on the surface either to inhibit reproduction or to kill the organism. Other strategies bind the active ingredient to the surface and kill only on contact. However, such surface binding strategies have been plagued by interference of the “soil load,” a layer of dead organisms or organic substances that physically block subsequent organisms from making contact with the bound active agents, effectively neutralizing the antimicrobial effect.

Eluting antimicrobial surfaces can utilize organic or inorganic antimicrobials. Commonly used organic antimicrobials include triclosan, tri butyl tin, oxybisphenoxarsine (OBPA), and zinc pyrithione. Such substances can be used effectively in many settings, but do not hold up well under high-wear or long-life applications and are relatively unstable under the high temperatures and pressures used in manufacturing. The most promising of the inorganic antimicrobials are the metals silver, copper and zinc, along with oxidative agents such as peroxides and reactive oxygen generators. Other inorganic compounds such as arsenic, mercury, and cadmium also have strong antimicrobial properties, but are biologically very toxic and are more difficult to deploy safely.

Silver, copper, and zinc all demonstrate significant antimicrobial activity with a wide therapeutic index. Of the three, silver is the least cytotoxic and the most potent against bacteria, being roughly 10 times as potent as copper. However, copper has a strong antifungal effect, thus combinations of copper and silver may be synergistic with respect to practical effectiveness. The antimicrobial effect of zinc is perhaps three orders of magnitude weaker than that of silver, and zinc most often is used in combination with silver.

Silver has a long history of use as an antimicrobial, with applications in water storage dating to the 5th century BC. Today silver is used regularly in water filtration media to control bacteria growth and prevent fouling of pipes and machinery due to the growth of biofilms. Silver compounds have long been used to prevent ophthalmia neonatorum due to Neisseria gonorrhoeae. Silver sulfadiazine creams have been widely accepted in burn therapy since the 1960s. Silver-eluting urinary catheters have been shown to reduce the incidence of catheter-associated infection. Silver has demonstrated antiviral activity against herpes simplex, vaccinia, influenza A and pseudorabies viruses in water. Silver also has antifungal activity, and has demonstrated a clinically significant ability to inhibit colonization of soft denture
materials with *Candida albicans*.\textsuperscript{81} Many other silver-containing substances are used in medicine.\textsuperscript{82}

Ionic silver is a broad spectrum antimicrobial to which bacteria show a low propensity to develop resistance.\textsuperscript{28} Silver has been found to interfere with sulfhydryl groups on enzymes involved with metabolism and proteins in the tissue structure of a microorganism. In addition, silver inhibits replication by binding to and denaturing bacterial DNA and RNA\textsuperscript{83, 84} suggesting a possible mechanism for inactivation of viruses. The observed strong antimicrobial efficacy of silver ions even at low concentrations is attributed to a strong tendency for bacteria to collect and concentrate silver.\textsuperscript{25}

Although silver is recognized as an effective antimicrobial, effective deployment requires the proper ionic species at the right concentration. Like organic antimicrobials, most silver compounds are too soluble, too insoluble, or too unstable in the chemistry of coatings, or cannot withstand the high temperatures used in the processing of plastics. Traditional elution chemistries are difficult to control, being strongly affected by temperature, flow, pH and the local chemical environment.

At least one durable, long-lasting, readily-engineered silver delivery mechanism is readily available in the form of zeolites, porous particles that are made from a particular formulation of inert aluminosilicate. Zeolites are heat-stable and can provide a consistent and effective delivery mechanism for inorganic antimicrobial agents while withstanding most industrial processes, including those used in the preparation and application of surface coatings and in the manufacture and extrusion of plastics.

The crystal structure of a zeolite results in an array of orthogonal, interconnected pores creating a regularly sized “skeletal” or “cage” structure (Figure 4). Zeolite pores are lined with negatively charged sites resulting from unsatisfied electrons in the aluminum-oxygen bonds of the aluminosilicate structure. As formed, these sites are occupied by sodium ions; however, a portion of them can be reversibly exchanged with silver and/or zinc ions.

![Figure 4: Model of the crystal structure of zeolite 4A. The blue spheres represent silver ions.](image-url)
A silver zeolite releases silver ions whenever common environmental cations such as sodium, calcium and potassium become available for exchange with the silver in the zeolite, resulting in controlled release. The environmental conditions favoring release of metallic ions at the surface are precisely those that would otherwise favor survival or growth of biologic pathogens on the surface.

The rate of release is further controlled because the ion exchange mechanism must be neutral with respect to charge, thus silver release cannot happen unless another ion takes its place on the zeolite. Silver elutes from the zeolite only in the presence of moisture, and only until the silver concentration reaches a local equilibrium value that happens to be in the right range of concentrations needed to kill bacteria, in the low parts-per-billion (µg/L) range. In very dry conditions in which microorganisms do not survive long or propagate, silver is not released. The duration of antimicrobial efficacy is thus enhanced because the active ingredient is not consumed when it is not needed.

The principal advantages of the zeolite vehicle are that the substance is stable under industrial and environmental conditions, and that free ions of the metal automatically are made available at the surface in an essentially constant concentration over periods of time that can be measured in decades. The ion delivery mechanism is so efficient that the total amount of inorganic metal is negligibly small, rendering such substances extremely safe, yet because of the physical attributes of the zeolite, the ion concentration at the surface can be reliably maintained within an effective killing range for many years. Silver zeolite coatings have been demonstrated effective against many different classes of microbes in a variety of settings.

Metal-containing zeolites are manufactured as a fine, talc-like powder that can be blended with coatings and plastics to impart antimicrobial activity in the same way as pigment powders are added to impart color. The technology can impart antimicrobial activity to nearly any manufactured product. Existing products utilizing these substances include refrigerators, water bottles, pools, ice-makers, curtains, carpets, clothing, catheters, doorknobs, and many other items. Silver zeolite coatings are recognized as safe: the FDA has approved silver zeolite materials for use in food packaging, and indwelling medical devices coated with silver zeolite have been classified by the FDA as class I, not requiring 510(k) application. Unfortunately, to date relatively few such antimicrobial environmental products have been produced specifically for use in hospitals.

The antimicrobial efficacy of silver-zinc zeolite powder can be directly evaluated using conventional minimum inhibitory concentration (MIC) test methods. Table 1 shows MIC values for a commercially-available zeolite (AgION) containing 2.5% Ag and 14% Zn, as tested against a variety of microorganisms.
Table 1: Minimum inhibitory concentrations (MIC) of silver/zinc zeolite against various organisms.

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (ppm or mg/L)</th>
</tr>
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<tbody>
<tr>
<td>E coli</td>
<td>62.5</td>
</tr>
<tr>
<td>P aeruginosa</td>
<td>62.5</td>
</tr>
<tr>
<td>S aureus</td>
<td>125</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>125</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>125</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>125</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>125</td>
</tr>
</tbody>
</table>

Loose zeolite powder has also been studied as a rinse for oral care. In one *in vivo* study, a mouth rinse dispersion containing 3% by weight of zeolite (2.5% Ag, 14% Zn) significantly inhibited plaque formation compared to controls\(^\text{94}\). In another study involving oral bacteria, the MIC of silver zeolite was evaluated for various bacteria under anaerobic conditions (Table 2)\(^\text{95}\).

Table 2: MIC values for silver/zinc zeolite against anaerobic oral bacteria. A range of MIC values corresponds to that measured for a variety of strains of the indicated organism.

<table>
<thead>
<tr>
<th>Periodontal Pathogens</th>
<th>MIC (ppm or mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyromonas gingivalis</td>
<td>256-512</td>
</tr>
<tr>
<td>Prevotella intermedia</td>
<td>256</td>
</tr>
<tr>
<td>Actinobacillus actinomyces comirans</td>
<td>256-512</td>
</tr>
<tr>
<td>Pathogens causing dental caries (cavities)</td>
<td></td>
</tr>
<tr>
<td>Streptococcus mutans</td>
<td>2048</td>
</tr>
<tr>
<td>Streptococcus sanguis</td>
<td>1024</td>
</tr>
<tr>
<td>Actinomyces viscosus</td>
<td>1024</td>
</tr>
</tbody>
</table>

Although MIC values demonstrate the basic efficacy of silver zeolite against various organisms, MIC values in bulk dispersion underestimate the real-world effectiveness of the same substance when used as an antimicrobial surface, because ion concentrations reach higher levels more rapidly in thin-film or droplet environments on a treated surface than they do in bulk dispersion. Quantitative surface area normalization of parameters is used to compare the results of dispersion and surface based antimicrobial studies: typical surface ion concentrations correspond to those produced by a bulk dispersion in liquid of approximately 30,000 mg/L of silver zeolite, or roughly 300 times the average MIC for silver zeolite in bulk dispersion when tested against common pathogenic bacteria.

A significant difference is seen when a direct comparison is made between surface and dispersion environments. Three different antimicrobial zeolites (Ag, Ag/Zn and Ag/Cu) were compared in a 0.01% dispersion (100 mg/L) at 1h, 4h and 24h after inoculation with *S. aureus* (Figure 5).\(^\text{96}\) A corresponding surface-based study then compared a control surface to an Ag-Zn zeolite coated surface against the same bacterial suspension (Figure 6).
A practical antimicrobial surface must continue to be effective in the face of significant soil loads, including those containing fats and oils, which can potentially inhibit ion release, bind ions and provide nutrients to the bacteria. When metal zeolite and control surfaces were coated with ground beef fat extract and then inoculated with *Listeria monocytogenes*, the treated
surfaces exhibited rapid reduction of microbial counts despite the soil load (Figure 7), in contrast to many other antimicrobial surfaces.\footnote{97}

![Figure 7: Reduction of \textit{Listeria monocytogenes} applied to a layer of beef fat extract on stainless steel with and without the Ag/Zn zeolite containing coating.](image)

It should be emphasized that laboratory investigations such as these are not designed to reflect the real-world performance of an antimicrobial surface. In the real world, bacteria on control surfaces usually decline over time, rather than surviving at steady state, mainly due to hostile environments. The killing time of antimicrobial surfaces is also correspondingly more rapid in the real world, as illustrated in Figure 8.

![Figure 8: Comparison of laboratory and real-world environments. Real-world die-off is accelerated for both control surfaces and treated surfaces.](image)

In one real-word investigation, a variety of metal zeolite coated surfaces were compared against uncoated stainless steel door push panels and sink faucet handles in a hospital.\footnote{98} Treated and untreated components were installed, and after 48 hours surfaces were swabbed for culture.
Figure 9 illustrates the significant difference that was seen between treated and untreated surfaces in overall bacterial colony counts 48 hours after installation.

Figure 9: Field study in a hospital demonstrating the reduction in surface bacteria achieved by Ag/Zn treated surfaces.

**Silver Zeolite and Human SARS-CoV virus**

Although silver zeolite has been previously shown effective against other coronaviruses, its effectiveness against SARS-CoV, the etiologic agent of SARS, has not previously been studied. SARS-CoV is known to be harder than many other coronaviruses, surviving at least 6 times longer than HCoV-229E (another human pathogen) in dried samples.48

Samples of commercially available silver zeolite (AgION powder, manufactured by Sinanen Co., Ltd.) were therefore sent for testing against the human SARS-CoV virus. Testing was performed at the Virosis Prevention Control Institute of the Chinese Center for Disease Control and Prevention.99

The MIC and inactivation tests were based upon bulk dispersion of the zeolite in cell culture medium. Samples of the zeolite were incubated with generation spreading kidney cells of the African green monkey (VERO E6) that had been experimentally infected with SARS-CoV-P11 and SARS-CoV-P8 strains of virus. Gancyclovir was used as a positive control.

The MIC for this silver zeolite was 94 mg/L at 2 and 4 hours, and 46 mg/L at 6 hours. The MIC for the positive control, gancyclovir, was 23.4 mg/L. At concentrations above 375 mg/L, the silver zeolite completely inactivated both strains of SARS-CoV within two hours (Figure 8). At concentrations above 188 mg/L the virus was completely inactivated within 6 hours. These results are comparable to those observed for other susceptible organisms.
Table 3: MIC values determined for Ag ion zeolite and a therapeutic antiviral drug in the human SARS-CoV study.

<table>
<thead>
<tr>
<th>Silver Zeolite/Virus Contact Time</th>
<th>MIC (ppm or mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>94</td>
</tr>
<tr>
<td>4 hours</td>
<td>94</td>
</tr>
<tr>
<td>6 hours</td>
<td>46.8</td>
</tr>
<tr>
<td><em>Ganciclovir Injected Antiviral Agent</em></td>
<td>23.4</td>
</tr>
</tbody>
</table>

Figure 10: Inactivation of human SARS-CoV virus by Ag ion zeolite at varying concentrations.

These tests were performed using bulk dispersion of silver zeolites to accommodate the standard cell culture methods used to assess viral activity. Real-world performance on contaminated surfaces depends on the metal ion concentration at the surface, which depends to a certain degree on the volume of the inoculum that is applied to a surface. Transfer of body fluids from an infected patient typically occurs either through direct contact (resulting in a thin film of material containing the virus) or via aerosolized droplets that settle onto surfaces. When thin-film and droplet models for SARS-CoV bearing materials are applied to a silver zeolite surface, the calculated concentrations of silver ion concentrations correspond to those produced by a bulk dispersion in liquid of approximately 30,000 mg/L of silver zeolite, well above the levels that have already been demonstrated effective in bulk solution.

Conclusions

Surface bio-contamination is a problem that contributes to community-acquired and nosocomial infection through episodic fomite transmission of disease and through persistent fomitic...
reservoirs. The extent to which fomitic reservoirs contribute to nosocomial infection is unknown, and additional work in this field could prove valuable.

Effective routine chemical disinfection is difficult because strong chemical solutions must be applied correctly and left in contact with surfaces for prolonged periods of time. Many materials are not amenable to such treatments, and many clinical environments do not accommodate them easily. Many fomitic reservoirs, such as pens, clipboards, and stethoscopes, are not routinely cleaned between patients.

Novel surface coatings offer the potential for self-decontamination through the controlled release of antimicrobial metal ions by non-toxic industrial coatings that can be applied to and incorporated within many different types of surfaces and materials.

Faster surface die-off of pathogens on a surface can significantly reduce the amount of time that a fomitic reservoir is capable of transmitting disease, and can also reduce the average surface population of pathogens available for transmission to a susceptible host.

An initial experimental study of SARS inactivation by a silver zeolite antimicrobial powder has shown inactivation in bulk suspension within as little as two hours. Silver zeolite surfaces routinely achieve surface silver ion concentrations much higher than those achieved in bulk suspension, thus likely can reduce the survival time of SARS on treated surfaces to two hours or less. This is a promising area for further investigation.
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