Antimicrobials In Healthcare

Dr. Gina Sloan

Summary

Healthcare Associated Infections (HAIs) are an increasing concern due to increased costs of medical care. Over the past years (from 2007 to 2014) there has been a push for hand hygiene compliance from CDC and WHO. Despite these efforts there remains low compliance to hand hygiene standards and indicates that additional measures are needed to continue to reduce HAIs. A system approach to combatting HAIs is needed that expands beyond simple hand hygiene compliance. The patient environment of care needs to be considered in order to provide a comprehensive solution to HAIs. This solution will continue to improve on hand hygiene, increase monitoring of environmental surfaces, introduce novel disinfection techniques, and utilize embedded antimicrobials.

The Environment of Care

The healthcare system represents a diverse and complex array of multiple interacting ecosystems. The healthcare system can be broken down into three distinct ecosystems:

1. The patient
2. The healthcare worker
3. The patient's environment

These ecosystems interact throughout the course of the day and of a patient's treatment cycle. The interplay of these ecosystems greatly impacts the ability of a patient to acquire a hospital-associated infection (HAI). Perhaps the most important ecosystem is that of the patient, followed by the healthcare worker, and patient environment. Current infection control strategies target a system based approach that addresses each ecosystem separately in the hope that reducing each contributing factor will in essence reduce overall HAI rates. To better understand each strategy and the implications of each strategy to overall HAI rates, each is addressed separately.

The Patient

The patient is the central focus of all healthcare. As such the patient represents a microcosm of social and environmental interactions that can result in the spread of microorganisms throughout the hospital. As a patient is diagnosed with a microbial infection, the first course of action is to prescribe an antibiotic to combat the infection within the patient. However, the patient remains infective for up to 24 hours after the first administration of the antibiotic. In fact, patients are continuously shedding bacteria on their skin, mucosal membranes (eyes, mouth, nose), and into their immediate surroundings (bedding, and different touch points).

The Healthcare Worker

Healthcare workers are able to pick up microbes that the patient has shed. There is a large push for hand hygiene measures within healthcare to help reduce the incidence of pathogens on healthcare workers. These are outlined by the Centers for Disease Control (CDC) and World Health Organization (WHO) [[1], [2], [3], [4]]. Hospitals are constantly creating innovative approaches to hand hygiene compliance and monitoring. These approaches have reduced HAI rates from 2007 until 2014 but there is still room for improvement [[5]].

Surprisingly, despite continued efforts to encourage hand hygiene compliance to reduce HAIs, there is still only a 40% compliance rate among healthcare workers. This means that 6 out of 10 times there is a missed opportunity for a healthcare worker to appropriately wash their hands [[6]]. The compliance rate was lowest when healthcare workers were touching patients' surroundings [[7], [8]]. This creates a new microcosm for infections to spread. If a healthcare worker missed a hand hygiene moment and then proceeds to the next patient, there is potential for the microorganisms that were shed by the first patient to be passed to the second patient. This can also occur on the hands and clothing of patient visitors that move from one room to the next.

The Patient Environment

The patient environment is a unique space that is being researched as a potential cause of HAI spread. As mentioned, the patient can shed bacteria onto inanimate objects within the hospital room [[9]]. Once on these dry inanimate objects, microorganisms have a remarkable ability to survive for days and even months. After a patient has been discharged, the hospital room must undergo a thorough cleaning, typically referred to as terminal cleaning. Terminal cleaning measures are meant to remove all microbes from the prior patient, presenting a microbial clean room to the next patient. However, despite best efforts, terminal cleaning continues to be inadequate. This results in an increased risk of HAI to the new patient representing 1.4X the risk for a Methicillin Resistant Staphylococcus aureus (MRSA) infection, 2.5X for a

---

1 Curtis, V., et al., ***Hygiene: new hopes, new horizons***. Lancet Infect Dis, 2011. 11(4): p. 312-21.

2 Aiello, A.E., et al., ***Effect of hand hygiene on infectious disease risk in the community setting: a meta-analysis***. Am J Public Health, 2008. 98(8): p. 1372-81.

3 Organization, W.H. ***Hand Hygiene: Why, How and When?*** Save Lives, Clean Your Hands 2009; Available from: http://www.who.int/gpsc/5may/Hand_Hygiene_Why_How_and_When_Brochure.pdf?ua=1.

4 Smith, S.J., et al., ***Where do hands go? An audit of sequential hand-touch events on a hospital ward***. J Hosp Infect, 2012. 80(3): p. 206-11.

5 CDC. ***National and State Healthcare Associated Infections: Progress Report. 2016***; Available from: https://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf.

6 Chemaly, R.F., et al., ***The role of the healthcare environment in the spread of multidrug-resistant organisms: update on current best practices for containment***. Ther Adv Infect Dis, 2014. 2(3-4): p. 79-90.

7 FitzGerald, G., G. Moore, and A.P. Wilson, ***Hand hygiene after touching a patient's surroundings: the opportunities most commonly missed***. J Hosp Infect, 2013. 84(1): p. 27-31.

8 Randle, J., A. Arthur, and N. Vaughan, ***Twenty-four-hour observational study of hospital hand hygiene compliance***. J Hosp Infect, 2010. 76(3): p. 252-5.

9 Weber, D.J., D. Anderson, and W.A. Rutala, ***The role of the surface environment in healthcare-associated infections***. Curr Opin Infect Dis, 2013. 26(4): p. 338-44.

Vancomycin Resistant Enterococcus(VRE) infection and 2.5X increased risk for a Clostridium difficile infection [6, [10], [11], [12], [13], [14], [15]].

Due to these increased carry over infection rates, the patient environment represents a new microcosm for infection transmission and a burgeoning subject of ongoing research. Dr. Cliff McDonald, from the CDC, has noted that there is a general limit of microorganisms on a surface that can be linked to an increased risk of a patient getting an HAI. Research is ongoing to determine develop a standard for environmental cleanliness [[16]]. In addition, Dr. Stephanie Dancer with National Health Services (NHS) in Scotland noted that hospitals should maintain a low microbial bioburden to ensure patient safety. Dr. Dancer proposed that hospitals monitor the bioburden on surfaces and maintain a bioburden that is < 5 bacteria per square centimeter [[17], [18]].

Current disinfection strategies such as spray and wipe disinfectants, hydrogen peroxide misting systems, and UV light disinfection systems represent discontinuous disinfection practices that do not provide adequate control of microbes in the environment. Current environmental control strategies are not able to meet the requirements set forth by either CDC or NHS. Therefore the environment must be approached via a system based mechanism that incorporates technologies that employ rapid kill rates via discontinuous mechanisms and technologies that are able to continuously provide microbial control measures throughout the day.

The Role of Antimicrobials in the Healthcare Environment

There is tremendous scrutiny given to antimicrobial usage in healthcare settings. Additionally, there are ongoing debates about the use of antimicrobials for healthcare within governmental agencies, industry and academia. It must first be acknowledged that there are 3 types of antimicrobials that are sometimes confused and inappropriately interchanged. These three classes of antimicrobials have different end uses and microbial targets. The three classes of antimicrobials are:

1. **Antibiotics**: utilized for treating patients with microbial based infections.
2. **Disinfection antimicrobials**: antimicrobials utilized in liquid or wipe applications that deliver high kill rates quickly but provides discontinuous microbial reduction.
3. **Embedded antimicrobials**: antimicrobials utilized for product preservation, odor control and the control of stain causing microorganisms and can offer continuous microbial reduction on a material.

Antibiotics

Antibiotics are governed by the Food and Drug Administration (FDA) and are meant solely for the treatment of humans

10 Otter, J.A., et al., ***Evidence that contaminated surfaces contribute to the transmission of hospital pathogens and an overview of strategies to address contaminated surfaces in hospital settings***. Am J Infect Control, 2013. 41(5 Suppl): p. S6-11.
11 Drees, M., et al., ***Antibiotic exposure and room contamination among patients colonized with vancomycin-resistant enterococci.*** Infection Control and, 2008.
12 Drees, M., et al., ***Prior environmental contamination increases the risk of acquisition of vancomycin-resistant enterococci***. Clin Infect Dis, 2008. 46(5): p. 678-85.
13 Nseir, S., et al., ***Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit***. Clin Microbiol Infect, 2011. 17(8): p. 1201-8.
14 Shaughnessy, M.K., et al., ***Evaluation of hospital room assignment and acquisition of Clostridium difficile infection***. Infect Control Hosp Epidemiol, 2011. 32(3): p. 201-6.
15 Huang, S.S., R. Datta, and R. Platt, ***Risk of acquiring antibiotic-resistant bacteria from prior room occupants***. Arch Intern Med, 2006. 166(18): p. 1945-51.
16 Shams, A.M., et al., ***Assessment of the Overall and Multidrug-Resistant Organism Bioburden on Environmental Surfaces in Healthcare Facilities***. Infect Control Hosp Epidemiol, 2016. 37(12): p. 1426-1432.
17 Dancer, S.J., ***How do we assess hospital cleaning? A proposal for microbiological standards for surface hygiene in hospitals***. Journal of Hospital Infection, 2004. 56(1): p. 10-15.
18 White, L.F., et al., ***Are hygiene standards useful in assessing infection risk?*** American Journal of Infection Control. 36(5): p. 381-384.

with a microbial infection. These drugs target specific organisms in a manner that is proven to be safe for the human. There are numerous classes of antibiotics that target different species and parts of the microorganism. For example, penicillin based antibiotics target the ability of a microorganism to reproduce its cellular membrane but quinolones interact with the ability to reproduce DNA. Based on the infection, the doctor will prescribe the required antibiotic for treatment. This type of treatment only impacts the patient, not the exposure of the healthcare worker or the environment to microbes.

Disinfection Antimicrobials

Disinfectants utilize antimicrobials that can reduce bacterial numbers quickly and are regulated via the Environmental Protection Agency (EPA). The EPA requires that hospital disinfectants kill all claimed microbes within 10 minutes. Most disinfectant companies, such as Clorox and EcoLab, exceed the EPA expectations with label claims within 2 minutes or less. These disinfectants are utilized throughout the hospital multiple times during the day. In most cases, bottles of disinfectant wipes can be found next to every bed and nurses station. These disinfectants act very quickly but do not offer long lasting protection. Research has demonstrated that with traditional disinfectants the microbes on the surface reach initial levels within 2 to 6 hours [[19]]. This results in an opportunity for HAI transmission despite typical disinfection practice.

Novel disinfectants are in development that allow for continuous disinfection within the healthcare setting that will allow for reduced bioburden levels across time. These have been tested by multiple academic institutions and will soon hit the market. Once these are widely available it will be possible to determine the role of continuous disinfection in reducing HAI rates.

Embedded Antimicrobials

Even with the promise of continuous disinfection within healthcare it is not reasonable to expect nurses or environmental services to clean every surface within each hospital room. The ability to provide continual microbial reduction can also be accomplished using antimicrobial treated articles [[20], [21]]. In general, these surface treatments last the life-span of the product and provide a means to continuously control microbial burden on the surface.

Embedded antimicrobials can be incorporated into polymer based substrates such as bed rails, high touch points such as light switches, powder coated door handles, nurses' stations and textile based materials such as bedding and gowns. Additionally, embedded antimicrobials can be utilized on single use, disposable, nonwoven products such as absorbent bed protectors. All of these applications are in intimate contact with the patient for the span of the patient's hospital stay, some are never changed or cleaned during that time period.

Embedded antimicrobials are specifically designed to provide the needed protection for a specific end use. For example, a hospital bed rail may utilize an antimicrobial that targets bacteria to reduce inherent bacterial load on the surface but a grout based material will target a mold to prevent discoloration of that surface. These antimicrobial surfaces are able to reduce the bioburden on the surface without causing concern for resistance development or negative health implications.

---

19 Attaway, H.H., 3rd, et al., ***Intrinsic bacterial burden associated with intensive care unit hospital beds: effects of disinfection on population recovery and mitigation of potential infection risk***. Am J Infect Control, 2012. 40(10): p. 907-12.
20 Salgado, C.D., et al., ***Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit***. Infect Control Hosp Epidemiol, 2013. 34(5): p. 479-86.
21 Schmidt, M.G., et al., ***Sustained reduction of microbial burden on common hospital surfaces through introduction of copper***. J Clin Microbiol, 2012. 50(7): p. 2217-23.

The utilization of these surfaces with disinfectant antimicrobials provides a system based approach to solving the problems associated with the patient environment being a vector for disease transmission [22].

Resistance Development

Typically patients that have bacterial or fungal infections will be prescribed antibiotics. Antibiotics are a type of antimicrobial that act upon very specific areas of the microbial cell. The specificity of the antibiotic to one cell component makes the development of resistance fairly easy for microbes that can reproduce within minutes and hours.

Embedded antimicrobials that are utilized for building materials, textiles and furnishings are very different. While safe, these antimicrobials are not meant for human consumption. Embedded antimicrobials are meant to act within the environment of the article.

Embedded antimicrobials are able to target multiple cellular components at the same time. In addition, this class of antimicrobials are able to target multiple organisms and sites on those organisms. This makes it very difficult to have resistance development build to these organisms. Academic, peer-reviewed literature supports that embedded antimicrobials do not cause a concern for microbial resistance development and propagation. In 2002 the EU concluded that "…there was no convincing evidence that Triclosan poses any risk to humans or to the environment by inducing or transmitting antibacterial resistance…[23]" A second study from 2003 delved into the presence of triclosan in sink drains. The authors were able to demonstrate that triclosan did not cause resistance within the inherent bacterial community [24]. This finding translates to a second group of antimicrobials, quaternary ammonium compounds, from a University of Manchester study indicated that the use of quaternary ammonium detergents at sub-lethal concentrations "did not significantly alter the distribution of susceptibility to QAC [quaternary ammonium compounds] or to a range of other biocides [25]." This view is supported by the Scientific Committee on Emerging and Newly Identified Risks that indicated the use of antimicrobials did not cause a link to antibiotic resistance or cause the development of pathogenic organisms.

The body of evidence from multiple regulatory bodies and academic groups indicates that the use of embedded antimicrobials is not linked to development of antibiotic resistance. These two classes of antimicrobials do not directly influence the same groups of microbes or act in similar manners. Embedded antimicrobials target multiple organisms, multiple cellular components, and have a role in the environment. It is for these reasons that embedded antimicrobials do not create resistance patterns that are shared with antibiotic resistance development for patients.

Embedded Antimicrobial Safety

The safety of antimicrobials is governed by the EPA and is broken into two main parts:

1. Antimicrobials that will be in contact with food and
2. Antimicrobials that will be non-food contact.

Once the use pattern, of food contact or non-food contact is determined, the safety of each pesticide is determined via

---

22 Page, K., M. Wilson, and I.P. Parkin, ***Antimicrobial surfaces and their potential in reducing the role of the inanimate environment in the incidence of hospital-acquired infections***. Journal of Materials Chemistry, 2009. 19(23): p. 3819-3831.
23 Products, S.C.o.C., ***Opinion on Triclosan***, H.C.P. Directorate-General, Editor. 2006.
24 McBain, A.J., et al., ***Exposure of Sink Drain Microcosms to Triclosan: Population Dynamics and Antimicrobial Susceptibility. Applied and Environmental Microbiology***, 2003. 69(9): p. 5433-5442.
25 McBain, A.J., et al., ***Effects of quaternary-ammonium-based formulations on bacterial community dynamics and antimicrobial susceptibility***. Applied and environmental microbiology, 2004. 70(6): p. 3449-3456.

a battery of tests that is specified through the Code of Federal Regulation [[26], [27]]. At a minimum each pesticide must pass a series of tests that target human health. These tests evaluate the ability of a pesticide to affect the skin, lungs, reproductive tract, and immune system. The pesticide is rated for each test and classified. Once classified a company must label products to indicate the associated hazard, if it exists. Based on the safety outcomes and the intended end uses, the EPA will review the appropriate use sites and then subsequently grant those to the company.

A company selling antimicrobials must operate within the provisions granted by the EPA. Incorporated antimicrobials offer an additional safety in that the antimicrobial is encapsulated within the end product, reducing exposure rates to both the environment and the person.

The making and marketing of antimicrobial products is highly regulated by the EPA. There is a federal statute that specifically governs this area, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). FIFRA allows the use of antimicrobials within products for product preservation, odor control and stain management caused by bacteria and mold. Companies are not allowed to market products with health claims (i.e. will Kill 99.9% of MRSA). Companies are obliged to follow these statutes or risk fines.

The safety of some legacy antimicrobials has been called into question lately. These antimicrobials, such as tin, arsenic and triclosan, offer a wide array of continually being replaced with greener more eco-friendly options. It is for this reason that embedded antimicrobial companies are already moving away from these compounds. Microban specifically has not utilized tin or arsenic and is not recommending the use of triclosan in any new customer applications.

Embedded Antimicrobial Efficacy

The efficacy of antimicrobial products must be demonstrated pursuant to FIFRA. A company must ensure that its products are efficacious when utilized per label instructions. The company must also develop and maintain data demonstrating the efficacy of each end product to be in compliance with FIFRA . EPA can request the data at any point.

To prove the efficacy of antimicrobials, efficacy protocols have been developed by numerous international and national standard organizations including but not limited to:

1. International Standards Organization (ISO)
2. American Standards and Test Methods (ASTM)
3. American Association of Textile Colorist and Chemists (AATCC)
4. Japanese Embedded Standard (JIS)

Protocols are developed with the input from numerous groups including companies, embedded end users and consumers. The general standards are developed with input from embedded and subject matter experts. For standards dealing with microorganisms, microbiologists from academia and industry gather together to work through method development. Each group works strenuously to develop methods that are robust, reproducible, and representative of efficacy throughout use. These methods go through rigorous review cycles that take years to have a final standard available for widespread use.

---

26 ***General Considerations for Uses of Antimicrobial Agents***, E.P. Agency, Editor. 2012: https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-810-product-performance-test-guidelines.

27 Office of Pesticide Programs, A.D., ***Applicability of the Treated Articles Exemption to Antimcirobial Pesticides***, P.R.N.P. 2000-1, Editor. March 6, 2000: https://www.epa.gov/pesticide-registration/prn-2000-1-applicability-treated-articles-exemption-antimicrobial-pesticides.

With the widespread adoption of antimicrobials in multiple industries, most organizations have a group dedicated to method development for antimicrobials specifically. It is through organizations like AATCC, ASTM and ISO, that there is effective self-policing throughout the industry. This is evident in peer-reviewed and approved test methods that allow reproducible demonstration of surface antimicrobial and product preservation attributes.

Efficacy is not solely attributable to one test that occurs immediately after manufacture. Once an antimicrobial is incorporated into an end product, that product endures multiple tests for durability. Durability tests are associated with each end use. An antimicrobial for a textile application will be rated based on durability to home launderings with commercially available detergents. A cutting board application will have durability to dish washing, and scraping whereas a grout will be exposed to multiple rounds of moisture exposure. Outdoor applications must also pass multiple rounds of intense UV exposure to ensure that the material is not affected and microbial efficacy is maintained.

Conclusions

There are multiple avenues that can lead to a reduction in HAI rates. These include adherence to strict handwashing regimens, vigilance over patient care, and care of the patient environment. Only by impacting all three areas of the healthcare ecosystem will a significant reduction in HAI rates be obtained.

Embedded antimicrobials have a role to play, along with disinfectants, in reducing bioburden in the patient environment. Embedded antimicrobial companies are engaging with researchers to initiate studies demonstrating the ability to integrate antimicrobial surfaces into an infection prevention strategy.