Antiseptic Stewardship: A Call to Action

For more than 4,000 years, mankind has been fascinated with cleaning and treating wounds in order to improve their chances for survival.[1-3] Infectious disease was, after all, the leading cause of death in the world.[4]

When the discovery of penicillin was made in 1928 by Sir Alexander Fleming, the simple observation that mold was bactericidal made history. Penicillin's introduction as a therapeutic agent was touted to be nothing short of a miracle drug. Sir Alexander Fleming clearly warned us in 1945 that we would see antibiotic resistance.[5] There it began, the use and misuse of a lifesaving medication.

Much has changed since Fleming, Chain, and Florey introduced and helped launch the first antibiotic commercially available some 70 years ago.[4] Today, we have a plethora of drugs available to combat most bacteria, as well as some viruses and fungi. Unfortunately, Fleming's warning continues to ring true today as antibiotic resistance has become one of the biggest threats to world health.[6] Bacterial resistance can be a natural occurrence, but improper use of antibiotics can accelerate its development.[6]

The public health crisis around the world has made antibiotic resistance a household name. The antibiotic resistance crisis and the antimicrobial stewardship era that it spawned have brought new scrutiny to the widespread use of antiseptic agents. Lessons learned from indiscriminate use of antibiotics are increasingly being applied to antiseptics as experts in the field caution that antiseptic resistance could be a natural consequence of injudicious antiseptic use.[7-10]

Table 1

Biocides and Antibiotics	Typical Uses and Characteristics
Antibiotic	Natural or synthetic drug given to prevent infections, or to kill or inhibit bacteria in a living host
Antiseptic	Chemical that kills or inhibits growth of microorganisms; applied to skin or living tissue
Disinfectant	Chemical that kills, inactivates or inhibits growth of microorganisms on inanimate surfaces
Preservative	Chemical that prevents the growth of microorganisms that can cause product deterioration

Sterilant	Chemical used to kill all vegetative and spore-forming microorganisms on multiuse and medical devices

Antiseptic Resistance

The use of commercially available topical and surface antiseptics, also referred to as biocides, has increased as a result of antibiotic resistance.[9] As practitioners "steward" antibiotic use, they naturally look to effective antimicrobial alternatives such as antiseptics, yet these products are susceptible to many of the same resistance pressures as antibiotics. Antiseptic resistance can be either a natural property of the organism or can occur as a result of acquisition or mutation.[12] Bacteria actually utilize the same protective resistance mechanisms against antiseptics/biocides, preservatives and disinfectants as they do against antibiotics.[9]

The challenge for clinicians today is two-fold: 1) there is a paucity of published studies evaluating *in vivo* antiseptic resistance, particularly in comparison to antibiotic resistance, and 2) antiseptic resistance is often poorly defined in the literature.[13] Historically, antimicrobial resistance was established using *in vitro* testing through various, and often, non-standardized methodologies evaluating the minimum inhibitory concentration (MIC).[14-18] However, the practice of using variable *in vitro* methodologies as well as sub-lethal MIC of a chosen antiseptic agent is proving to be problematic. This is best explained by examining the case for one of the most commonly used antiseptics, chlorhexidine gluconate (CHG), a potent, broad-spectrum agent used in a vast number of applications.

Identifying Chlorhexidine Resistance

The term "chlorhexidine resistance" is often discussed by proponents of antiseptic stewardship, but it is a generally poorly understood concept for two important reasons: there is currently no consensus on the definition of chlorhexidine "resistance," nor is there a standardized method for detecting it.

Drug resistance testing involves collecting bacterial RNA, converting it into DNA through a series of processes, and then amplifying it through polymerase chain reaction (PCR). Researchers use an *in vitro*, direct observation process called phenotyping to assess how well a test agent (e.g., drug or antiseptic) will work against a specific bacterium. Genotyping is used to predict how the test agent will work against a specific bacterium. When both genotyping and phenotyping results are combined, a clearer result on resistance is either established or it is not.

Genotypic Testing

Genotypic susceptibility testing evaluates the gene sequencing of the bacterium. A multitude of genes have been identified that confer resistance to chlorhexidine. The most well-known and described are the efflux pump-encoding genes such as *qacA* and *qacB*.[8] Efflux pumps are

transport proteins located on the cytoplasmic membrane of the bacteria that allow the bacteria to literally "pump" chlorhexidine out of the cell. In fact, efflux pumps function to move and expel a broad range of antibiotics, chemicals, dyes, and antiseptics from the cell.[19,20] In so doing, they serve as a vital survival mechanism for the bacteria.[20]

While detection of these and other resistance genes provide clues about potential resistance, it is not definitive resistance testing. Research has shown the presence of these genes does not guarantee that the organism will display phenotypic resistance to chlorhexidine just as the absence of the genes does not guarantee susceptibility.[8]

Phenotypic Testing

In vitro phenotypic testing of chlorhexidine has frequently been performed using inferior concentrations than one would expect to be achieved with an *in vivo* clinical application. For example, a number of studies have used a mean inhibitory concentration of > or = to 4mg/L for chlorhexidine resistance.[8] Organisms that survive at a sub-lethal CHG concentration will not be able to withstand concentrations that occur with actual clinical use concentrations (e.g., 40000 mg/L in 4% aqueous chlorhexidine solution).[8] MICs and mean bactericidal concentrations (MBCs) describe concentrations reachable in body fluids which are not necessarily relevant to antiseptics used on intact skin.[8]

A Worrisome Trend

Over the past decade, a number of studies have identified both genotypic and phenotypic resistance to CHG among clinical bacterial isolates. Not surprisingly, this resistance appears to correlate with increased CHG usage. In a genotypic study of the skin commensal coagulase negative staphylococci, researchers found the prevalence of the efflux pump resistance genes *qacA/B* to be significantly higher among nursing staff than among the general population (57% vs 14%, respectively; p<0.001), presumably because of exposure to CHG within the hospital environment.[21] In a 2017 study of patients with CHG-impregnated dressings for prevention of CLABSI, researchers demonstrated a high prevalence of the CHG resistance genes *qacA/B* (67%) and *smr* (18%) among DNA specimens recovered from the skin of patients with central venous catheters.[22] Additionally, there was a statistically greater proportion of *qac*-positive specimens collected from patient sites with greater than 72 hours of exposure to CHG dressings than from those with shorter exposure to CHG dressings (p=0.04).[22] A 2019 NIH-sponsored study of pediatric oncology patients from 37 centers throughout the US and Canada receiving daily CHG bathing led to the identification of a *qacA* variant*, qacA4*, that confers even further reduced susceptibility to CHG raising the question of whether frequent use of CHG leads to selection for *qacA4*.[23]

In a study of phenotypic CHG susceptibility (defined as an MIC of greater than or equal to 4 µg/ml based on earlier studies) among organisms causing central line-associated bloodstream infections (CLABSI) at the Johns Hopkins Hospital, researchers found a 69% prevalence of

reduced CHG susceptibility irrespective of patients' bathing status (CHG vs no CHG).[24] However, in units where patients received daily CHG bathing, organisms causing CLABSI were more likely to have reduced CHG susceptibility than CLABSI-causing organisms in units where CHG bathing was not performed (86% vs. 64%, p=0.028).[24] A study of MRSA isolates in a hospital where 4% CHG had been used for hand hygiene for over 20 years revealed that the percentage of isolates with a CHG MIC greater than or equal to 4µg/ml increased from 1.7% in 1990 to 46.7% in 2005.[25] A British study demonstrated that use of CHG for MRSA decolonization led to selection for a MRSA strain with a CHG mean bactericidal concentration that was three times that of the other MRSA strains found in the facility.[26]

Cross-Resistance

Recently, researchers have discovered that some of the plasmid-borne efflux pump genes which confer degrees of resistance to CHG may also confer some resistance to certain antibiotics.[10,27,28] Additionally, CHG resistance genes have a shared location with some antimicrobial resistance genes on the same mobile genetic elements.[8]

Over the past few years, several in vitro studies have identified potential cross-resistance between CHG and several potent antibiotics. In a study of 237 *Staphylococcus aureus* clinical isolates, Zhang et al identified a significant association between isolates carrying the *qacA/B* genes and resistance to ciprofloxacin (p=0.005), trimethoprim/sulfamethoxazole (p=0.001), clindamycin (p=0.023), and tetracycline (p=0.01).[29]

An *in vitro* study by Wand et al demonstrated that adaptation of clinical *Klebsiella pneumoniae* isolates to CHG exposure not only lead to "stable resistance to chlorhexidine, but also cross-resistance to [the last-resort antibiotic] colistin," prompting the authors to caution that "the fact that increased colistin and chlorhexidine resistance may occur in clinical isolates without significant loss of fitness/virulence highlights the potential challenges associated with critical infection control procedures and the use of chlorhexidine as an antiseptic to control health care-associated infections."[10]

A chemical that constantly stresses bacteria to adapt, and behaviors that promotes antibiotic resistance needs to be stopped immediately when the benefits are null.

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Bhardwaj et al exposed vancomycin-resistant *Enterococcus faecium* (VREfm) strains to increasing concentrations of CHG over 21 days and identified not only reduced susceptibility to CHG but reduced susceptibility to the antibiotic daptomycin.[7] The authors postulate that because evidence demonstrates that CHG concentrations on patient skin can fall below the MIC for VREfm between patient bathing, selection for mutants with reduced susceptibility to CHG and other antimicrobials may occur.[7] They conclude that "frequent improper use of CHG (i.e. the presence of subinhibitory concentrations on patient skin) may favor the emergence and persistence of these VREfm mutants in healthcare settings."

Antiseptic Stewardship

The Association for Professionals in Infection Control and Epidemiology (APIC), The World Health Organization (WHO), The Centers for Disease Control and Prevention (CDC) and many other organizations and governmental institutions worldwide are actively engaged in educating about the danger of the overuse and misuse of antimicrobial agents. Great strides have been made in implementing antibiotic stewardship in acute care facilities and, in fact, in 2019, the Joint Commission just informed outpatient centers of their needs to implement a similar program by 2020. While the primary focus of these antimicrobial stewardship efforts has been antibiotics, antiseptics have largely been unaddressed. There is an urgent need to develop coordinated programs which promote and evaluate the appropriate use of *both* antibiotics *and* antiseptics.

Many healthcare facilities have instituted a series of infection prevention interventions, also called bundles, that include CHG to reduce the rate of hospital acquired infections (HAIs),[30] but the evidence is not clear-cut in their favor. Take, for example, the practice of patient bathing with CHG to reduce HAI acquisition. The evidence is conflicting. In a study of roughly 7,700 ICU patients published in 2013, Climo et al demonstrated a significant reduction in HAIs with daily CHG bathing.[31] By contrast, in a study published in 2015 of over 9,300 ICU patients, Noto et al demonstrated that daily bathing with CHG had no significant impact on reducing HAIs.[32] Most recently, in the largest study of its kind to the authors knowledge (n=339,902), Huang et al demonstrated that daily bathing with CHG in combination with targeted mupirocin for MRSA carriers did not significantly reduce multi-drug resistant organisms in non-ICU patients.[33] This conflicting evidence, viewed through the lens of antiseptic stewardship, should prompt all institutions to re-evaluate practices that employ broad use of antiseptics. As Kampf stated in his 2016 review of acquired resistance to CHG, "...it seems to make sense to restrict the valuable agent CHG to those indications with a clear patient benefit and to eliminate it from applications without any benefit or with a doubtful benefit."[9]

For other practices, the evidence may be more robust in their favor, but the benefits must be weighed against the potential risks. The practice of universal decolonization with nasal mupirocin and CHG bathing for methicillin-resistant *Staphylococcus aureus* has been shown to be effective in reducing MRSA HAIs,[34] but the risk of promoting CHG resistance is a very real one. In a recent study published in the *American Journal of Infection Control,* Eed et al identified a significantly higher prevalence in phenotypic CHG resistance among methicillin-resistant coagulase-negative staphylococci (MR-CoNS) isolates when universal decolonization with

mupirocin and CHG was employed compared with no decolonization.[35] The authors caution that because transfer of resistance genes between MR-CoNS and other pathogens is known to occur, CHG resistance in MR-CoNS could have broader implications for CHG resistance in other nosocomial pathogens.[35]

As we have done with antibiotics, all antiseptic use, no matter where or how much, must be evaluated and alternatives agents should be chosen if antimicrobial biocides are not shown to demonstrate an evidence-based benefit. This is no easy task. Compliance with established evidenced-based antimicrobial use practices should be monitored and evaluated. Training should take place to ensure proper use. Careful patient monitoring is a cornerstone for optimal patient outcomes. Product selection should be based on infection reduction, avoidance of adverse events, patient and staff satisfaction, resources needed for implementation and use, and patient outcomes. Product costs should not be the driving factor, rather it should be a later consideration. Alternative products, which promote a healthy patient and environmental microbiome, should always be considered whenever the evidence supports it.

There are some signs that antiseptic stewardship is gaining traction. In 2016, the FDA announced a ban on a group of 19 antimicrobial/biocidal chemicals.[36] The FDA asked manufacturers to provide data for evidence that their biocide-containing soaps, for example, were more effective than plain soap. These biocides were being used extensively, not just in soaps, but in a plethora of consumer products, from cosmetics to plastics, without restriction. Unfortunately, these biocides are now ubiquitous in our environment—detectable in water supplies and soils.[36]

Conclusion

While current testing methodologies are limited in their ability to measure antiseptic resistance, *in vitro* studies clearly demonstrate the potential for bacteria to develop antiseptic resistance. The clinical impact of this potential remains to be seen, but waiting "to see" makes no sense in a historical context. The lessons taught us by the antibiotic resistance crisis must be applied to antiseptic use if we want to avoid "history repeating itself." Consideration for the development of antiseptic resistance and, more worryingly, cross-resistance between antiseptics and antibiotics, should be given when establishing antiseptic use protocols—much as we wish had been done for antibiotics several decades ago. As Albert Einstein so aptly stated, the definition of insanity is doing the same thing over and over again and expecting different results.

Theraworx Protect is a topical immune health system that can help you manage healthcare-associated risks while supporting your facility's antimicrobial stewardship program. Find out more at TheraworxProtect.com.

References

1. Brown, H., *Wound Healing Research Through The Ages*, ed. D. Cohen, and Lindblad. 1992, Philadelphia: WB Saunders.

2. Shah, J.B., *The history of wound care.* J Am Col Certif Wound Spec, 2011. 3(3): p. 65-6.
3. Carmicheal, A.G. and R.M. Ratzan, *Medicine: A Treasury of Art and Literature*, ed. H.L. Levin. 1991, New York, NY.
4. Kardos, N. and A.L. Demain, *Ernst Chain: a great man of science.* Applied Microbiology and Biotechnology, 2013. 97(15): p. 6613-6622.
5. Oppenheimer, J., *Alexander Fleming: The Man and the Myth. Gwyn Macfarlane.* The Quarterly Review of Biology, 1985. 60(2): p. 200-201.
6. WHO. *Antibiotic Resistance*. 2019 [cited 2019 June 21]; Available from: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance.
7. Bhardwaj, P., et al., *Reduced Chlorhexidine and Daptomycin Susceptibility in Vancomycin-Resistant Enterococcus faecium after Serial Chlorhexidine Exposure.* Antimicrobial agents and chemotherapy, 2018. 62(1).
8. Horner, C., D. Mawer, and M. Wilcox, *Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter?* The Journal of antimicrobial chemotherapy, 2012. 67(11): p. 2547-2559.
9. Kampf, G.n., *Antiseptic stewardship: biocide resistance and clinical implications*. 2018, Springer: Cham, Switzerland.
10. Wand, M.E., et al., *Mechanisms of Increased Resistance to Chlorhexidine and Cross-Resistance to Colistin following Exposure of Klebsiella pneumoniae Clinical Isolates to Chlorhexidine.* Antimicrobial agents and chemotherapy, 2017. 61(1).
11. Sheldon, A.T., Jr., *Antiseptic "Resistance": Real or Perceived Threat?* Clinical Infectious Diseases, 2005. 40(11): p. 1650-1656.
12. McDonnell, G. and A.D. Russell, *Antiseptics and Disinfectants: Activity, Action, and Resistance.* Clinical Microbiology Reviews, 1999. 12(1): p. 147-179.
13. Jones, R.D., *Bacterial resistance and topical antimicrobial wash products.* American Journal of Infection Control, 1999. 27(4): p. 351-363.
14. Russell, A. and N. Russell, *Biocides: activity, action and resistance.* 50 Years of antimicrobials., ed. P. Hunter, G. Darby, and N. Russell. 1995, United Kingdom: Society for General Microbiology.
15. Day MJ, R.A., *Bacterial sensitivity and resistance. Methicillin-resistant staphylococci. .* Principles and practice of disinfection, preservation and sterilization. 1992, England: Oxford.
16. Sivaji, Y., et al., *Disinfectant induced changes in the antibiotic sensitivity and phage typing pattern in Staphylococcus aureus.* Journal of Hospital Infection, 1986. 7(3): p. 236-243.
17. Prince, H.N., et al., *Drug resistance studies with topical antiseptics.* Journal of Pharmaceutical Sciences, 1978. 67(11): p. 1629-1631.
18. Brumfitt, W., S. Dixson, and J.M.T. Hamilton-Miller, *Resistance to antiseptics in methicillin and gentamicin resistant Staphylococcus aureus.* The Lancet, 1985. 325(8443): p. 1442-1443.
19. Sun, J.J., Z.Q. Deng, and A.X. Yan, *Bacterial multidrug efflux pumps: Mechanisms, physiology and pharmacological exploitations.* Biochemical and Biophysical Research Communications, 2015. 465(1): p. 165-165.

20. Bay, D.C. and R.J. Turner, *Small Multidrug Resistance Efflux Pumps*. 2016, Switzerland: Springer International Publishing.
21. Zhang M, O'Donoghue MM, Hiramatsu K, Boost MV. Prevalence of antiseptic-resistance genes in Staphylococcus aureus and coagulase-negative staphylococci colonizing nurses and the general population in Hong Kong. J Hosp Infect 2011; 78(2): 113-7.
22. Choudhury MA, Sidjabat HE, Rathnayake IU, Gavin N, Chan RJ, Marsh N, et al. Culture-independent detection of chlorhexidine resistance genes *qacA/B* and *smr* in bacterial DNA recovered from body sites treated with chlorhexidine-containing dressings. J Med Microbiol 2017; 66: 447-453.
23. Addetia A, Greninger AL, Adler A, Yuan S, Makhsous N, Qin X, et al. A novel, widespread *qacA* allele results in reduced chlorhexidine susceptibility in *staphylococcus epidermis*. Antimicrob Agents Chemother 2019; 63(6): e02607-18.
24. Suwantarat N, Carroll KC, Tekle T, Ross T, Maragakis LL, Cosgrove SE. et al. High prevalence of reduced chlorhexidine susceptibility in organisms causing central line-associated bloodstream infections. Infect Control Hosp Epidemiol 2014; 35(9): 1183-186.
25. Wang JT, Sheng WH, Wang JL, Chen D, Chen ML, Chen YC, et al. Longitudinal analysis of chlorhexidine susceptibilities of nosocomial methicillin-resistant *Staphylococcus aureus* isolates at a teaching hospital in Taiwan, J Antimicrob Chemother 2008; 62(3): 514-17.
26. Batra R, Cooper BS, Whitely C, Patel AK, Wyncoli D, Edgeworth JD. Efficacy and limitation of a chlorhexidine-based decolonization strategy in preventing transmission of methicillin-resistant Staphylococcus aureus in an intensive care unit. Clin Infect Dis 2010; 50(2): 210-7.
27. DeMarco, C.E., et al., *Efflux-Related Resistance to Norfloxacin, Dyes, and Biocides in Bloodstream Isolates of Staphylococcus aureus.* Antimicrobial Agents and Chemotherapy, 2007. 51(9): p. 3235-3239.
28. Wassenaar, T.M., et al., *Review and phylogenetic analysis of qac genes that reduce susceptibility to quaternary ammonium compounds in Staphylococcus species.* European journal of microbiology & immunology, 2015. 5(1): p. 44-61.
29. Zhang, Y., et al., *Chlorhexidine exposure of clinical Klebsiella pneumoniae strains leads to acquired resistance to this disinfectant and to colistin.* International Journal of Antimicrobial Agents, 2019. 53(6): p. 864-867.
30. Calfee, D.P., et al., *Strategies to prevent transmission of methicillin-resistant Staphylococcus aureus in acute care hospitals.* Infect Control Hosp Epidemiol, 2008. 29 Suppl 1: p. S62-80.
31. Climo, M.W., et al., *Effect of daily chlorhexidine bathing on hospital-acquired infection.* The New England journal of medicine, 2013. 368(6): p. 533-542.
32. Noto M.J., et al., *Chlorhexidine bathing and healthcare-associated infections: a randomized clinical trial.* JAMA, 2015. 313(4): p. 369-378.
33. Huang, S.S., et al., *Chlorhexidine versus routine bathing to prevent multidrug-resistant organisms and all-cause bloodstream infections in general medical and surgical units (ABATE Infection trial): a cluster-randomised trial.* The Lancet, 2019. 393(10177): p. 1205-1215.

34. Huang S.S., et al., Targeted versus universal decolonization to prevent ICU infection. New England Journal of Medicine, 2013. 368: p. 2255-2265.

35. Eed E.M., et al. Prevalence of mupirocin and chlorhexidine resistance among methicillin-resistant coagulase-negative staphylococci isolated during methicillin-resistant *Staphylococcus aureus* decolonization strategies. American Journal of Infection Control, 2019. In Press.

36. McNamara, P.J. and S.B. Levy, *Triclosan: an instructive tale.* Antimicrobial agents and chemotherapy, 2016. 60(12): p. 7015-7016.