

***Clostridioides difficile* Infection Prevention: The Role of Patient Bathing and Issues With Current Practice**

Introduction: Burden of CDI

In 2013, the Centers for Disease Control and Prevention (CDC) named infection with *Clostridioides difficile* (*C.difficile*) as one of the three most urgent antibiotic resistant threats to human health in the U.S.¹ Infections caused by *C. difficile* are estimated to affect half a million Americans each year and, according to data from the CDC, approximately 15,000 of those infections will end in death.²⁻³ The latest National Healthcare Safety Network data reported a 13 percent statistically significant decrease in *C.difficile* infections (CDIs) among acute care hospitals in the U.S. between 2016 and 2017,⁴ but these infections remain a significant cause of morbidity and mortality and continue to be a major target for local and national infection prevention efforts.⁵

Background: Core Elements of CDI Prevention

Core elements of CDI prevention include antimicrobial stewardship, rapid identification and diagnosis, and prevention of CDI transmission.⁶⁻⁷ Antibiotics are a leading risk factor for CDIs, particularly fluoroquinolones and 3rd and 4th generation cephalosporins.⁶⁻⁷ Antibiotic stewardship programs (ASPs) are designed to promote appropriate selection, dose, route, and duration of treatment and multiple studies have demonstrated reductions in CDI incidence when ASPs have been implemented.⁸ Rapid diagnosis is a critical component of CDI prevention because it leads not only to prompt treatment but also to swift implementation of contact precautions that can limit pathogen spread.⁹ CDIs have presented a diagnostic challenge over the years, but recent guidance from the Infectious Disease Society of America (IDSA) and The Society for Healthcare Epidemiology of America (SHEA) has standardized diagnostic pathways, facilitating more accurate diagnosis.¹⁰

Because *C.difficile* is highly transmissible, a multimodal approach is necessary for effective transmission prevention.⁶⁻⁷ Isolation measures, contact precautions, and hand hygiene protocols are fundamental to preventing disease spread by direct contact.^{6-7,10} Placing affected patients in private rooms with a dedicated toilet and patient-care equipment such as stethoscopes and blood pressure cuffs, mandating healthcare workers (HCWs) don gloves and gowns prior to patient care, and establishing robust hand hygiene protocols with compliance measurement can reduce patient-patient and patient-HCW transmission.^{6-7,10} Arguably as important is prevention of indirect transmission via the patient care environment.⁶⁻⁷ Research has shown that *C. difficile* spores can survive on inanimate surfaces for up to 5 months¹¹ and are resistant to some of the most commonly used hospital disinfectants (e.g., quaternary ammoniums and phenolics),¹²⁻¹³ leading to recommendations for daily and terminal use of Environmental Protection Agency (EPA) List K sporicidal agents in the rooms of affected patients.^{6,14} The CDC additionally recommends consideration of ancillary disinfection with no-touch technologies.⁶

The Role of Patient Bathing in CDI Transmission Prevention

Rationale

Another element of CDI transmission prevention found in multiple CDI prevention guidelines, including those of the CDC, IDSA/SHEA, and Association for Professionals in Infection Control and Epidemiology (APIC), is patient bathing.^{6-7,10,15} The rationale behind it is a logical one: to reduce the burden of spores on a patient's skin.¹⁰ Patients with CDI frequently have heavy skin contamination with *C. difficile* spores on multiple body areas, not only during active infection but up to 4 weeks after resolution of diarrhea.¹⁶⁻¹⁸ Multiple studies have demonstrated the efficacy of patient bathing protocols in reducing infections with other pathogens including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus,¹⁹ but the hearty *C. difficile* spores present a much greater challenge.²⁰

Evidence: A single-agent and a paucity of studies

Soap and water are considered the gold standard of hand hygiene for spore removal, but in fact are only moderately effective, with much of the effect attributed to mechanical removal.¹⁶ Studies have demonstrated that soap and water handwashing results in the removal of only 2 log₁₀ colony forming units of spores or less from hands.^{16,21-24} Full-body bathing for spore removal, particularly with a bed-ridden patient, is an even greater challenge. A 2011 study of bed bathing with soap and water did not result in significant reductions of spores on the skin of patients with CDIs.²⁰

One of the most often used alternatives to soap and water bathing is bathing with the antiseptic chlorhexidine gluconate (CHG).²⁵ CHG patient bathing has been shown to reduce the rate of a number of healthcare-associated infections (HAIs), but the data on CDI reduction is extremely limited. A pub med literature search for the terms "patient bathing" and "*C. difficile*" or "*Clostridium difficile*" or "*Clostridioides difficile*" produced 6 publications evaluating the impact of bathing on CDI incidence.²⁶⁻³¹ Of the six studies, all evaluated CHG bathing (bathing with CHG-impregnated cloths, CHG bed basin baths or showers) and only one study, a quasi-experimental study, documented a reduction in CDI rates.²⁶⁻³¹ In the only published randomized clinical trial, Noto et al found that "daily bathing with chlorhexidine did not reduce the incidence of healthcare-associated infections including ... *C. difficile*."²⁶

A closer examination of CHG for CDI patient bathing might shed some light on these results. Under normal conditions, CHG is not sporicidal.¹⁶ CHG's antimicrobial effect is achieved via disruption of vegetative organisms' cell wall and plasma membrane, both of which are shielded by tough proteinaceous coats in bacterial spores, rendering them immune to CHG.³²⁻³³ In fact, in a study of the effect of different bathing protocols on skin microbiota in ICU patients, Cassir et al observed a greater rate of colonization with sporulating bacteria among those receiving CHG bathing compared with those receiving soap and water bathing (p=0.019).³⁴ Nerandzic and colleagues demonstrated susceptibility of *C. difficile* spores to CHG when exposed to temperatures of 80 degrees Celsius (176 degrees Fahrenheit), when combined with 70% ethanol, and when ambient pH was elevated to 9.5 or higher; however, these combinations are clearly not compatible with patient skin.³² Additionally, CHG is contraindicated for the perineum,³⁵ in

theory the body area where the greatest concentration of spores would be found and thus the area most in need of effective cleaning.

One could argue that CHG bathing might be viewed through the same lens as alcohol-based hand hygiene products for CDI prevention in non-outbreak settings. Despite the superior efficacy of soap and water over alcohol-based products for *C.difficile* spore removal, the IDSA and SHEA do not preferentially recommend soap and water hand hygiene for CDI prevention in non-outbreak settings.³⁶ This is based on the fact that no studies to date have documented an increase in CDI rates in non-outbreak settings when alcohol-based products are used for hand hygiene, while studies have demonstrated reductions in other pathogens when these products are used.³⁶ The same could be said of CHG bathing for CDI prevention. There are no studies to date that have documented a significant increase in CDI rates when CHG is used for patient bathing, while studies have been published demonstrating reductions in other HAIs. However, before that logic can be applied, there are several factors related to CHG that should be considered.

CHG: Adverse Events

Since its initial commercial availability in the UK in 1954 and later introduction in the U.S. in the 1970s, CHG use for antiseptics has grown exponentially.³⁷ In 2013 one regional hospital in Massachusetts reported 17 different applications for CHG in their facility which did not include the longstanding application of gingival or periodontal antiseptics.³⁸ As use of CHG becomes more widespread, so have reports of adverse events.³⁸⁻⁴⁰ These events range from mild irritant contact dermatitis to delayed or immediate hypersensitivity reactions to full-blown anaphylactic shock and were the basis for the FDA's recent warning about CHG allergic reactions in 2017.³⁸⁻⁴¹ Existing database numbers are still relatively small, but experts agree that the numbers are on the rise and are likely underdiagnosed and/or underreported.³⁸⁻⁴⁰ In a 2013 review of adverse reactions to CHG published in *Dermatitis*, the authors report that when CHG is included in allergen series patch testing, positive results are seen in 0.5 to 13.1% of the studied population.³⁸ In a review of perioperative severe allergic reactions to CHG, it was determined that the majority of patients had experienced some minor symptom upon previous exposure to CHG suggesting sensitization.³⁹ Indeed, cases of perioperative anaphylaxis are thought to represent one of the largest areas for underreporting of CHG allergy because of the multitude of factors that can cause intraoperative hypotension.³⁸⁻³⁹

CHG: Reduced Susceptibility

Another consideration for CHG bathing in CDI prevention is that of antiseptic resistance. Reports of increasing tolerance/reduced susceptibility to CHG among clinical isolates are on the rise, as are reports identifying the presence of CHG resistance genes.^{33,42-49} Efforts to quantify the prevalence of "CHG resistance," however, are hampered by the fact that there is neither a consensus on what defines CHG resistance nor a standardized method for detecting it.³³ Current methods used to identify reduced susceptibility to CHG include phenotypic-based methods (e.g., mean inhibitory concentration [MIC]) and genotypic-based methods (e.g., molecular identification of resistance genes).^{33,43-44,46-49} A number of studies are identifying a disturbing trend toward both increased phenotypic and genotypic detection of CHG resistance within the acute care setting.^{33,42-49}

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).⁴³ 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%, $p=0.028$).⁴³ 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 2005.⁴⁹ 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.⁴⁸

Genotypic studies have identified similar patterns. A study of the efflux pump resistance genes *qacA/B* in the skin commensal coagulase negative staphylococci found the prevalence 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.⁴⁷ 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.⁴² 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 ($p=0.04$).⁴² 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*.⁴⁴

Not surprisingly, the growing body of evidence pointing to reduced susceptibility to CHG with increasing use has prompted cautionary warnings from experts in the field regarding indiscriminate use of the valuable antiseptic.^{33-34,45} In a 2016 review of acquired resistance to CHG, Kampf advised:

- "...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."⁴⁵

Likewise, in their review of reduced susceptibility to CHG in staphylococci, Horner et al caution:

- "Indiscriminate chlorhexidine use in the absence of efficacy data should be discouraged."³³

These statements raise the question of whether it is judicious to use a valuable antiseptic for prevention of CDI transmission if it is:

- 1) not sporicidal,
- 2) lacking high-quality evidence supporting its efficacy in transmission prevention,
- 3) associated with an increasing risk of allergy, and
- 4) potentially reducing efficacy of the antiseptic in applications where it has proven benefit

Bathing in CDI Transmission Prevention: Finding an Alternative to CHG

Patients with CDI have several bathing needs: soil removal, spore reduction, and, in many cases, skin optimization due to the perineal inflammation that can occur with diarrhea. In evaluating alternatives to CHG for patient bathing in CDI transmission prevention, several key factors should be considered:

- **Efficacy:** Is the product sporicidal? Is there robust time kill data for the product against *C. difficile* spores?
- **Adverse Events:** What is the product's safety profile? Does it contain ingredients that are often allergenic?
- **Skin Compatibility:** How does the product affect skin health? Does the product influence the skin's own immunoregulatory functions? Incontinence-associated dermatitis (IAD) can be a debilitating complication of *C. difficile* infection. Does the product have an impact on IAD outcomes? Does it promote healthy acidic skin pH which not only enhances epithelialization and tissue oxygenation but inhibits pathogen growth and increases macrophage and fibroblast activity?
- **Resistance:** Is the potential for resistance to the product a concern?

Theraworx Protect: A Novel Topical Immune Health System

Theraworx Protect is a multi-ingredient skin formulation designed to reduce macro and micro debris from skin while simultaneously supporting the skin's acid mantle and supporting the natural antimicrobial functions of the skin's outermost layer, the stratum corneum.⁵⁰⁻⁵¹ The inherent acidic nature of the stratum corneum is actually a key component of skin function and health, influencing barrier homeostasis, stratum corneum cohesion and integrity, antimicrobial defense mechanisms, and wound healing.⁵²⁻⁵³ The normal pH of healthy skin, which ranges from pH 4-6, activates lipid-processing enzymes that synthesize ceramides, critical components of the skin's permeability barrier.⁵² By contrast, an alkaline pH not only downregulates these enzymes but also activates serine proteases involved in the desquamation and degradation of the proteins responsible for skin cohesion.⁵² Accordingly, studies have shown that the skin barrier is disrupted when the pH is elevated.⁵⁴⁻⁵⁵

Acidic pH is also critical to our skin's innate immunity.⁵²⁻⁵³ Normal, healthy skin commensals thrive in acidic pH levels, while pathogenic bacteria thrive in higher pHs.⁵² An acidic pH also enhances macrophage and fibroblast activity while reducing activity of bacteria-produced proteases and therefore levels of the toxic end-products they release.⁵²⁻⁵³ Even a natural antimicrobial peptide found in sweat, dermicidin, is a far more potent antimicrobial in an acidic milieu than in a neutral or alkaline environment.⁵² Equally as important is that an acidic

environment enhances tissue oxygenation, epithelialization, and angiogenesis—all critical elements in wound healing.⁵³

Using a product for patient skin cleansing that optimizes the stratum corneum has obvious benefits for reduction nosocomial risks. Traditional bathing products, however, do not provide this stratum corneum support. Soap-based cleansers are alkaline and possess a higher potential for skin irritation including stratum corneum swelling and lipid rigidity.^{52,56} In an IRB, randomized-controlled study comparing Theraworx Protect to CHG in a repeated application testing model, CHG was shown to actually degrade the stratum corneum.⁵⁰ Compromising this layer of the skin can be a significant factor when it comes to managing healthcare-associated conditions. Take, for example, a patient with a pressure ulcer in the ICU. Bathing that individual with a product that is potentially harmful to their outer skin layer is obviously going to be counterproductive to both preventing infection and promoting wound healing.

In the case of CDI, skin optimization is of even greater importance because of the risk of moisture-associated skin damage such as IAD. IAD can cause pain, burning, and itching that impact a patient's sleep and mobility.⁵⁷ The loss of mobility increases their risk for pressure injury and the breakdown of skin increases their risk of infection, setting the stage for a vicious cycle.⁵⁷ Urine and/or feces on the skin increase the skin pH to alkaline which creates an environment conducive to bacterial growth.⁵⁷ Digestive enzymes in the stool cause skin breakdown.⁵⁷ All of this allows bacteria and other organisms in the stool to thrive in that environment. The problem with current IAD treatment technologies is that they don't restore the natural acidic pH of the skin, so the alkaline pH continues to allow growth of pathogenic organisms.⁵⁷

The Theraworx Protect protocol helps to address the risks associated with these problems with one product. It cleans and helps to create a low-pH environment that is inhospitable to multi-drug resistant organisms, yeast, and fungi.⁵⁰⁻⁵¹ It protects and supports the skin barrier.⁵⁰⁻⁵¹ It restores and maintains the normal acidic pH of healthy skin, helping to bolster skin integrity, support natural stratum corneum defense mechanisms, and support conditions that promote wound healing.⁵⁰⁻⁵¹ It is also inexpensive and incredibly easy to use. For CDI patients, impregnated wipes can be used for patient bathing to reduce spore burden. For patients with IAD, a spray formulation can be applied to the affected area—which is far more comfortable for patients and less traumatic to the irritated skin. The product can then air dry with no need to rinse.

Conclusion

Patient bathing is just one of many important CDI transmission measures, but it is one that deserves more careful examination. The one-size-fits-all approach often employed with CHG use may not be the best strategy when it comes to patient bathing, and consideration should be given to novel products that demonstrate efficacy, support skin health and immunity, and assist antiseptic stewardship efforts.

Theraworx Protect Topical Immune Health System can help you manage healthcare-associated risks while supporting your facility's antimicrobial stewardship program. Find out more at TheraworxProtect.com.

References

- 1) Centers for Disease Control and Transmission. Antimicrobial resistance: biggest threats and data. Available from: https://www.cdc.gov/drugresistance/biggest_threats.html#cdiff. Accessed 11 June 2019.
- 2) Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. *N Eng J Med* 2015; 372(9): 825-834.
- 3) Centers for Disease Control and Prevention. Healthcare-associated infections: *Clostridioides infection*. Available from: https://www.cdc.gov/hai/organisms/cdiff/cdiff_infect.html. Accessed 7 June 2019.
- 4) Centers for Disease Control and Prevention. Healthcare-associated infections: current HAI progress report. Available from: <https://www.cdc.gov/hai/data/portal/progress-report.html>. Accessed 5 June 2019.
- 5) Centers for Disease Control and Prevention. Healthcare-associated infections: the targeted assessment for prevention (TAP) strategy. Available from: <https://www.cdc.gov/hai/prevent/tap.html>. Accessed 7 June 2019.
- 6) Centers for Disease Control and Prevention. Healthcare-associated infection: strategies to prevent *Clostridioides difficile* infection in acute care settings. Available from: <https://www.cdc.gov/hai/prevent/cdi-prevention-strategies.html>. Accessed 7 June 2019.
- 7) Health Research & Educational Trust. Preventing *C.difficile* infection and transmission: 2017 update. Available from: <http://www.hret-hiin.org/Resources/cdi/17/clostridium-difficile-infection-cdi-change-package.pdf>. Accessed 5 June 2019.
- 8) Centers for Disease Control and Prevention. Antibiotic use for healthcare: antibiotic use in hospitals and long-term care. Available from: <https://www.cdc.gov/antibiotic-use/healthcare/evidence/asp-int-cdiff.html>. Accessed 5 June 2017.
- 9) Bartlett J, Gerding D. Clinical Recognition and Diagnosis of *Clostridium difficile* Infection. *Clin Infect Dis*. 2008; 46 (Suppl 1): S12-S18.
- 10) McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66(7): e1-e48.

- 11) Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infect Dis.* 2006;6:130. Published 2006 Aug 16. doi:10.1186/1471-2334-6-130
- 12) Mayfield JL, Leet T, Miller J, Munday LM. Environmental control to reduce transmission of *Clostridium difficile*. *Clin Infect Dis* 2000; 31(4): 995-1000.
- 13) Wilcox MH, Fawley WN. Hospital disinfectants and spore formation by *Clostridium difficile*. *Lancet* 2000; 356(9238): 1324.
- 14) Environmental Protection Agency. List K: EPA's registered antimicrobial products effective against *Clostridium difficile* spores. Available from: <https://www.epa.gov/pesticide-registration/list-k-epas-registered-antimicrobial-products-effective-against-clostridium>. Accessed 10 June 2019.
- 15) Association for Professionals in Infection Control and Epidemiology. Preventing transmission of *Clostridium difficile* in healthcare settings. 2011. Available from: https://apic.org/Resource_/TinyMceFileManager/Practice_Guidance/cdiff/2013_C_diff_final_Fishbone_Diagram_11x17.pdf. Accessed 9 June 2019.
- 16) Nerandzic MM, Rackaityte E, Jury LA, Eckart K, Donskey CJ. Novel strategies for enhanced removal of persistent *Bacillus anthracis* surrogates and *Clostridium difficile* spores from skin. *PLoS One.* 2013;8(7):e68706. Published 2013 Jul 2. doi:10.1371/journal.pone.0068706
- 17) Sethi AK, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. *Infect Control Hosp Epidemiol* 2010; 31(1): 21-7.
- 18) Bobulsky GS, Al-Nassir WN, Riggs MM, Sethi AK, Donskey CJ. *Clostridium difficile* skin contamination in patients with *C. difficile*-associated disease. *Clin Infect Dis* 2008; 46(3): 447-50.
- 19) Climo MW, Sepkowitz KA, Zuccotti G, Fraser VJ, Warren DK et al. (2009) The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter study. *Crit Care Med* 37: 1858-1865
- 20) Jury LA, Guerrero DM, Burant CJ, Cadnum JL, Donskey CJ. Effectiveness of routine patient bathing to decrease the burden of spores on the skin of patients with *Clostridium difficile* infection. *Infect Control Hosp Epidemiol.* 2011; 32: 181-184.
- 21) Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD (2009) Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of *Clostridium difficile* . *Infect Control Hosp Epidemiol* 30: 939-944

- 22) Jabbar U, Leischner J, Kasper D, Gerber R, Sambol SP et al. (2010) Effectiveness of alcohol-based hand rubs for removal of *Clostridium difficile* spores from hands. *Infect Control Hosp Epidemiol*; 31: 565-570.
- 23) Weber DJ, Sickbert-Bennett E, Gergen MF, Rutala WA (2003) Efficacy of selected hand hygiene agents used to remove *Bacillus atrophaeus* (a surrogate of *Bacillus anthracis*) from contaminated hands. *JAMA* 289: 1274-1277.
- 24) Edmonds SL, Zapka C, Kasper D, Gerber R, McCormack R et al. (2013) Effectiveness of hand hygiene for removal of *Clostridium difficile* spores from hands. *Infect Control Hosp Epidemiol* 34: 302-305.
- 25) Sturgeon LP, Garrett-Wright D, Lartey G, Jones MS, Bormann L, House S. A descriptive study of bathing practices in acute care facilities in the United States. *Am J Infect Control* 2019; 47(1): 23-26.
- 26) Noto MJ, Domenico HJ, Byrne DW, Talbot T, Rice TW, Bernard GR. Chlorhexidine bathing and healthcare-associated infections: a randomized clinical trial. *JAMA* 2015; 313(4): 369-378.
- 27) Bui LN, Swan BA, Olsen RJ, Long SW, Graviss EA. Chlorhexidine bathing and *Clostridium difficile* infection in a surgical intensive care unit. *J Surg Res* 2018; 228: 107-111
- 28) Kengen R, Thoonen E, Daveson K, Loong B, Rodgers H, Beckingham W, et al. Chlorhexidine washing in intensive care does not reduce bloodstream infections, blood culture contamination and drug-resistant microorganism acquisition: an interrupted time series analysis. *Crit Care Res* 2018; 20(3): 231-240.
- 29) Kassakian SZ, Mermel LA, Jefferson JA, Paranteau SL, Machan JT. Impact of chlorhexidine bathing on hospital-acquired infections among general medical patients. *Infect Control Hosp Epidemiol* 2011; 32(3): 238-43.
- 30) Popovich KJ, Hota B, Hayes R, Weinstein RA, Hayden MK. Effectiveness of routine patient cleansing with chlorhexidine gluconate for infection prevention in the medical intensive care unit. *Infect Control Hosp Epidemiol* 2009; 30(10): 959-63.
- 31) Rupp ME, Cavaliere RJ, Lyden E, Kucera J, Martin M, Fitzgerald T, et al. Effect of hospital-wide chlorhexidine patient bathing on healthcare-associated infections. *Infect Control Hosp Epidemiol* 2012; 33(11): 1094-100.
- 32) Nerandzic MM, Donskey CJ. Induced sporicidal activity of chlorhexidine gluconate against *Clostridium difficile* spores under altered physical and chemical conditions. *PLoS One* 2015; 10(4): e0123809.

- 33) Horner C, Mawer D, Wilcox M. Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? *J Antimicrob Chemother* 2012; 67(11): 2457-2559.
- 34) Cassir N, Papazian L, Fournier PE, Raoult D, La Scola B. Insights into bacterial colonization of intensive care patients' skin: the effect of chlorhexidine daily bathing. *Eur J Clin Microbiol Infect Dis* 2015; 34: 999-1004.
- 35) Drugs.com. Chlorhexidine topical. 2017. Available from: <https://www.drugs.com/mtm/chlorhexidine-topical.html>. Accessed 18 June 2019.
- 36) Society for Healthcare Epidemiology of America. Rationale for hand hygiene recommendations after caring for a patient with *Clostridium difficile* infection 2011. Available from: <https://www.shea-online.org/images/patients/CDI-hand-hygiene-Update.pdf>. Accessed 8 June 2019.
- 37) ChlorhexidineFacts.com About chlorhexidine: history of chlorhexidine. Available from: <https://chlorhexidinefacts.com/history-of-chlorhexidine.html>. Accessed 11 June 2019.
- 38) Silvestri DL, McEnery-Stonelake M. Chlorhexidine: uses and adverse reactions. *Dermatitis* 2013; 24(3): 112-118.
- 39) Abdallah C. Perioperative chlorhexidine allergy: is it serious? *J Anaesthesiol Clin Pharmacol* 2015; 31(2): 152-154.
- 40) U.S. Food and Drug Administration. FDA drug safety communication: FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate. 2017. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-rare-serious-allergic-reactions-skin-antiseptic>. Accessed 6 June 2019.
- 41) Garvey LH, Kroigaard M, Poulsen LK, Skov PS, Mosbech H, Venemalm L, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; 120(2): 409-15.
- 42) 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.
- 43) Suwantararat 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.

- 44) 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.
- 45) Kampf G. Acquired resistance to chlorhexidine—is it time to establish an ‘antiseptic stewardship’ initiative? *J Hosp Infect* 2016; 94(3): 213-227.
- 46) Alam MM, Kobayashi N, Uehara N, Watanabe N. Analysis on distribution and genomic diversity of high-level antiseptic resistance genes *qacA* and *qac B* in human clinical isolates of *Staphylococcus aureus*. *Microb Drug Resist* 2003; 9(2): 109-21.
- 47) 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.
- 48) 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.
- 49) 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.
- 50) Paulson DS, Topp R, Boykin RE, Schultz G, Yang Q. Efficacy and safety of a novel skin cleansing formulation versus chlorhexidine gluconate. *Am J Infect Control* 2018; 46(11): 1262-1265.
- 51) Wiemken TL, Kelley RR, Carrico RM, Binford LE, Guinn BE, Mattingly WA, et al. Efficacy of a novel skin antiseptic against carbapenem-resistant Enterobacteriaceae. *Am J Infect Control* 2015; 43(4): 380-382.
- 52) Ali SM, Yosipovitch G. Skin pH: from basic science to basic skin care. *Acta Derm Venereol* 2013; 93: 261-267.
- 53) Nagoba BS, Suryawanshi NM, Wadher B, Selkar S. Acidic environment and wound healing: a review. *Wounds* 2015; 27(1): 5-11.
- 54) Hachem JP, Crumrine D, Fluhr J, Brown BE, Feingold KR, Elias PM. pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. *J Invest Dermatol* 2003; 121: 345–353.

- 55) Hachem JP, Man MQ, Crumrine D, Uchida Y, Brown BE, Rogiers V, et al. Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. *J Invest Dermatol* 2005; 125: 510–520
- 56) Ananthapadmanabhan KP, Lips A, Vincent C, Meyer F, Caso S, Johnson A, et al. pH-induced alterations in stratum corneum properties. *Int J Cosmet Sci* 2003; 25: 103–112
- 57) McNichol LL, Ayello EA, Phearman LA, Pezzella PA, Culver EA. Incontinence-associated dermatitis: state of the science and knowledge transition. *Adv Skin Wound Care* 2018; 31(11): 502-513.