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Chlorhexidine-based decolonization to reduce healthcare-associated infections and multidrug-resistant organisms (MDROs): who, what, where, when, and why?

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Summary

Body surface decolonization with chlorhexidine bathing and nasal mupirocin has become a simple solution for prevention of healthcare-associated infections. The clinical trial evidence for this practice will be reviewed to understand who benefits from this practice, for what reasons, and at what times. The method of bathing and nasal decolonization will also be discussed as proper application is needed for maximal effectiveness. Finally, the conflict between current effectiveness and future potential for fueling resistance is considered.

Introduction

From its inception, the medical profession has been steeped in a deep desire to treat, cure, and prevent suffering. A great deal of the diseases that have long occupied us involve contagion. Despite centuries of exceptional progress in thwarting infections, we still strive to conquer the unabating remnant of pathogens that plague us.

In that infinite journey, there have been inspirations so simple that they evoke disbelief prior to being widely adopted as best practice. Once adopted, there is an equally fervent disbelief that the historical reality was ever perceived as acceptable. For infection prevention, some of these transformative innovations for preventing healthcare-associated infections include hand hygiene to prevent puerperal fever, [1] surgical sterility and skin preparation,[2,3] alcohol-based hand sanitizer, [4] and sealed urinary catheters [5].

Likewise, the simple concept of using antiseptics for full body bathing and showering has been broadly adopted in healthcare for high-risk patient populations to prevent infection. This concept was pioneered by those who saw potential for infection prevention beyond its effective use for hands and pre-operative skin preparation.

While there are several antiseptic products available for body bathing (e.g. bleach, chlorhexidine, tea tree oil, octenidine, and others), this discussion will focus on recent large-scale studies and trials involving full body chlorhexidine (CHG) bathing to reduce healthcare-associated infections (HAIs) and multidrug resistant organisms (MDROs). These studies often include nasal decolonization products, such as 2% mupirocin nasal ointment and 10% povidone-iodine, because of their ability to address the nasal reservoir (and thereby body reservoir) of

Staphylococcus aureus, while CHG is more broadly active and can reduce body bioburden from a wide variety of human pathogens and commensals.

A brief history of CHG in tribute to Edward Lowbury

CHG was first discovered in the early 1950s by a chemical company in the United Kingdom, and was rapidly commercialized as a broadly active antiseptic in 1954 [6]. Its mechanism of action is based upon cationic properties, which allow disruption of microbial cell surfaces and cell death at concentrations as low as 0.01%. Dr. Edward Joseph Lister Lowbury was the first to perform comparative effectiveness studies of soap, CHG, and other antiseptics for single and repeated hand and focal pre-operative skin disinfection [7-11]. He was also the first to describe their differential effects on removing superficial bacterial skin contamination and removing resident bacteria that surfaces from deeper skin layers [12-14]. His work was later extended by his colleague and successor Graham Ayliffe, who was among the first to study the benefits of CHG for pre-surgical full body bathing [15,16].

Initially, and for many decades, CHG was used in healthcare for focal skin and mucosal cleansing. It was commonly used as a hand antiseptic at concentrations of 4% or less, and also in dilute form for dental hygiene to treat periodontitis [17]. Eventually, published trials codified the superiority of CHG over povidone-iodine for skin disinfection prior to central line placement and surgical incision, both with and without con-current alcohol [18-22].

The work by Ayliffe and others on full body antiseptic bathing ultimately led to the universal recommendation for full body pre-operative antiseptic bathing in the 1999 US Healthcare Infection Control Practices Advisory Committee (HICPAC) surgical site infection guidelines [23]. This experience opened the door to pioneering efforts by Robert A. Weinstein who was the first to explore the value of routine daily full body CHG bathing to pre-vent infections in intensive care units (ICUs) [24e27]. For the purposes here, the term decolonization refers to the use of CHG for full body bathing or showering with or without concomitant nasal products to reduce carriage of *S. aureus*.

Why decolonize in healthcare facilities?

The drive to decolonize as a strategy to reduce infections and MDROs in healthcare arose from public and provider outcry that HAIs unnecessarily occur because of failure to perform preventative steps, some of which are yet to be discovered. The response to this outcry was a genuine quest to achieve the lowest possible levels of HAI e striving for zero cases for greater and greater lengths of time.

Decolonization focuses on bacterial carriage as an endogenous source of infection in highly vulnerable individuals and situations. It is well known that humans extensively shed bacterial pathogens, which then contaminate the environment and provide a series of opportunities for spreading pathogens to others (Figure 1). Several infection prevention activities counter these opportunities, but it is notable that decolonization works upstream of the event cascade, thereby pre-venting the shedding of pathogens, [27] preventing contamination of the

environment and healthcare worker hands, [24] preventing acquisition of multidrug-resistant organisms (MDROs) and other pathogens, and ultimately pre-venting infection [25,26].

Another important reason to favour decolonization as one of several critical infection prevention strategies is because it is the only strategy that helps those who already harbor MDROs. Most infection prevention strategies (e.g. environmental cleaning, hand hygiene, contact precautions, active screening) are designed to prevent spread of MDROs (or other pathogens) to those who do not yet harbour them. Decolonization provides a universal approach by protecting both MDRO carriers and non-carriers. This is increasingly important in most hospitals, where an increasing proportion of patients asymptomatically harbour MDROs over time. In the United States, nearly 15% of hospitalized patients asymptomatically harbor an MDRO, [28] with higher estimates in ICUs [29,30]. Admission prevalence of resistant gram-negative bacteria alone is 10% among German tertiary care centers [31,32]. In nursing homes or care homes for the elderly, estimates range from 10-20% in Belgium, Germany, and Spain [33-35];20-30% in the UK and Hong Kong [36,37];40-65% in the US [38-41]; and up to 80% in Italy as well as US long-term acute care hospitals [38,42].

Furthermore, decolonization with topical CHG is superior to regular soap not only because of its antiseptic properties, but also because it binds to skin proteins and continues to exert its antiseptic activities on the skin for up to 24 hours [27,43-45]. Hence, the concept of daily CHG bathing is intended to provide continuous protection from HAIs during a hospital stay. This is in contrast to alcohol-based hand hygiene or soap and water where lack of residual activity allows contamination to occur when touching objects or people immediately after use.

In the next section, the findings of CHG decolonization trials will be discussed. These trials and other studies show that topical CHG bathing has a legacy of preventing infections due to pathogens for which the skin is not the primary body reservoir. For example, among MDROs, the primary reservoir of meticillin-resistant *S. aureus* (MRSA) is the nose, and the primary reservoir for vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase producers (ESBL), and carbapenem-resistant Enterobacteriaceae (CRE) is the gut. Nevertheless, study after study demonstrates that topical decolonization of the skin (with or without addressing the nasal reservoir) can prevent a significant portion of healthcare-associated infections from these and other pathogens in a wide array of patient populations. This emphasizes the importance of skin integrity and cleanliness for preserving health due to endogenous and exogenous pathogen threats.

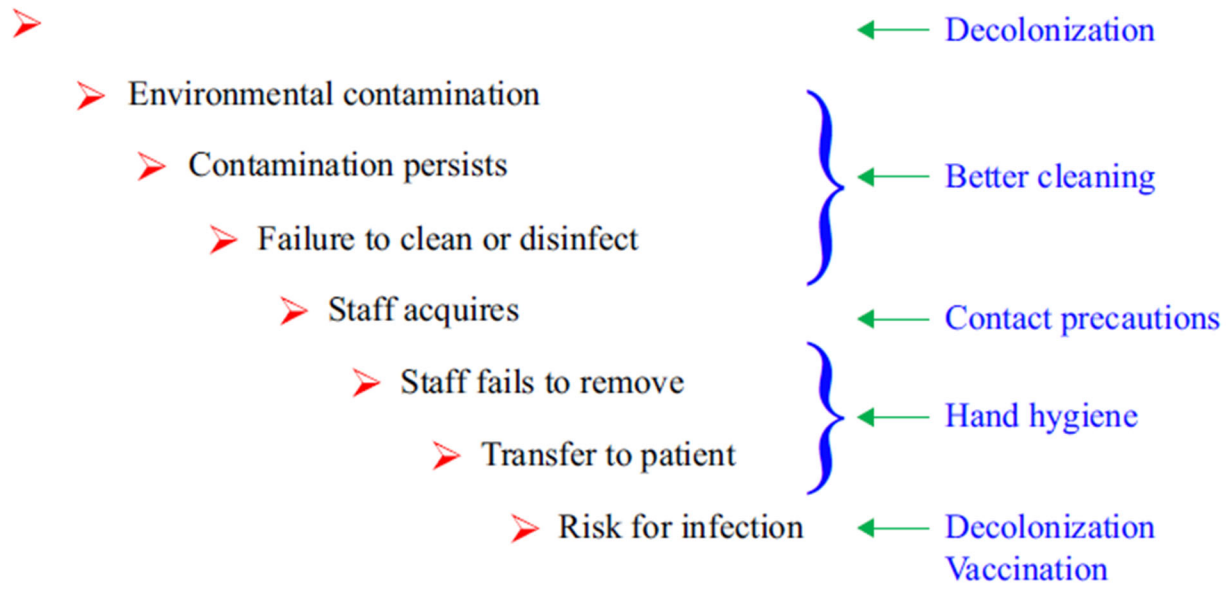

Figure 1. Figure displaying a series of events that enable patient-to-patient transmission of pathogens to occur along with their associated risk of healthcare-associated infection. Also displayed are common infection prevention strategies to mitigate these events.

Who should receive CHG decolonization?

CHG decolonization is a strategy for those at high risk for infection. These include those who are vulnerable because of host characteristics or circumstance. Initial trials for CHG decolonization were focused on **targeted decolonization for secondary prevention** in those with recurrent episodes of *S. aureus* disease [46]. In the past decade, large-scale randomized trials (Table I) have shifted focus to **targeted decolonization for primary prevention**, and then ultimately to **universal decolonization for primary prevention**.

The targeted CHG decolonization trials for primary prevention of infection focused on *S. aureus* carriers identified through rapid screening of inpatients, most of whom were undergoing surgery. Those harboring *S. aureus* were decolonized with CHG bathing and nasal mupirocin. Bode et al. compared decolonization to placebo among 917 *S. aureus* carriers identified by admission screening of predominantly surgical patients. Those receiving decolonization had significantly fewer inpatient *S. aureus* infections, especially deep surgical site infections [47]. These findings suggest that CHG and mupirocin confer benefit when given both pre- and post-operatively, because the surgery could occur anytime during the 5 day decolonization regimen. In contrast, Harbarth et al compared the value of admission MRSA screening to no admission screening in over 10,000 surgical patients in a hospital where decolonization of MRSA carriers was routine. The additional identification of MRSA carriers from screening did not reduce total hospital-associated MRSA infection [48].

In 2013, several universal decolonization trials for primary prevention of MDROs and infection in ICUs were published and expanded the evidence for HAI and MDRO reduction in patient populations at high risk for infection [49-51]. This led to wide-spread adoption of daily CHG bathing, with and without nasal decolonization, in the US and UK [58-61] Decolonization trials extending outside ICUs then followed. The ABATE Infection Trial found that universal decolonization in non-critical care units reduced MDROs and bloodstream infections only in the subset of patients with medical devices [53]. This raised natural questions about the targeted role of decolonization for protection of medical devices throughout the continuum of care. Furthermore, targeting MRSA carriers with repeated rounds of CHG and mupirocin decolonization in the CLEAR Trial reduced MRSA infections and hospitalizations following hospital discharge [54]. Finally, recent large scale trials in nursing homes have shown that universal decolonization, but not targeted decolonization, can significantly reduce MDRO prevalence [55-57].

In a brief departure from large-scale randomized controlled trials, the US CDC has been investing in regional prevention of MDROs through decolonization. The SHIELD Orange County Project was a 38 healthcare facility project in Orange County, California that involved CHG bathing and nasal iodophor for universal decolonization in nursing homes and long-term acute care facilities, and targeted decolonization of patients in contact precautions in hospitals [38,62,63]. All 17 participating hospitals were already routinely performing universal ICU decolonization. Across the 25-month SHIELD intervention, MDRO prevalence declined by 24% in long-term care facilities and by 14% among hospitalized patients in contact precautions [62].

What Products Should be Used?

When used for bathing, chlorhexidine concentrations of 2% and 4% are most commonly used. The 4% formulation is generally applied and rinsed off in the shower while 2% CHG is used as a leave-on product for bed bathing. As an applicator, a mesh sponge enables CHG to lather well for the shower since lathering is difficult through hand rubbing alone. Furthermore, non-cotton applicators are important since cotton binds CHG and limits its release to the skin [43].

The 2% leave-on product is favored because it results in higher residual concentrations of CHG on the skin, which then provide germicidal activity for up to 24 hours [43]. The 4% formulation is too drying to be used as a leave-on product, but the 2% concentration is well-tolerated. Safety has been well demonstrated with over a million baths being conducted during clinical trials, with a <1%-2% risk of mild skin reactions that resolve rapidly upon discontinuation [49-51,53,54]. Anaphylaxis is rare, but has been reported in case reports.

Nasal decolonization in combination with CHG has usually involved 2% mupirocin ointment. However, reports of mupirocin resistance in some geographic areas has led to the recent evaluation of 10% povidone-iodine in some clinical trials [52,56].The Mupirocin-Iodophor Swap Out Trial will directly evaluate the non-inferiority of universal ICU decolonization with CHG-iodophor compared to CHG-mupirocin for the outcomes of ICU-attributable *S. aureus* clinical cultures and all-cause bacteraemia. In the meantime, nasal

iodophor has been shown to be effective in reducing MRSA carriage when universally used with CHG bathing in nursing homes [57,62]. In both the Swap Out Trial and these other decolonization studies, nasal iodophor was given twice daily for five days, similar to mupirocin, because of evidence that a single dose is only suppressive and daily dosing is inferior to twice daily dosing [64,65].

Table I

Large-scale randomized clinical trials evaluating CHG decolonization to reduce infection and MDRO[a]

Trial and Target Population	N	Intervention	Impact of Decolonization
Pre-Operative Use			
Bode et al [47]	918	Universal inpatient screening for *S. aureus*. Carriers randomized to CHG and mupirocin vs routine care	Among *S. aureus* carriers, 58% less inpatient *S. aureus* infection, including 79% less deep surgical site infection
Harbarth et al [48]	10,844	Universal inpatient screening for MRSA. Carriers randomized to CHG and mupirocin vs routine care	No difference in overall hospital-associated MRSA infection
Intensive Care Units			
Climo et al [49] 6 Academic medical centers	7727	Universal CHG bathing vs routine care	23% less MRSA/VRE ICU acquisition (as treated)
REDUCE MRSA Trial [50] 43 Community hospitals	74,256	A. Targeted CHG and mupirocin for MRSA carriers B. Universal CHG and mupirocin C. Routine care	37% less MRSA ICU clinical cultures 44% less all-cause ICU bloodstream infection
Pediatric SCRUB Trial [51] 5 Academic medical centers	4947	Universal CHG bathing vs routine care	36% less ICU bloodstream infection (as treated)
Mupirocin Iodophor Swap Out [52] 137 Community hospitals	~250,000	A. Universal CHG and mupirocin B. Universal CHG and iodophor	Results pending
Non-Intensive Care Units			
ABATE Infection Trial [53] 53 Community hospitals	339,902	Universal CHG bathing plus targeted mupirocin for MRSA carriers vs routine care	No difference in MRSA/VRE clinical cultures or bloodstream infection in overall non-ICU population In subset with medical devices: 37% less MRSA/VRE clinical cultures 32% less bloodstream infection (post-hoc analysis)
Post-Discharge			
CLEAR Trial [54]	2121	Targeted education plus 5 day course of CHG bathing, CHG mouthwash, and mupirocin repeated twice a month for six months vs education alone for MRSA carriers	In the year following discharge: 30% less MRSA infection 17% less all-cause infection
Nursing Homes			
Bellini et al [55]	4750	Universal screening for MRSA followed by targeted CHG bathing, CHG mouthwash, nasal mupirocin, and room disinfection for MRSA carriers vs routine care	No difference in one-day MRSA point prevalence
Protect Trial [56,57] 28 Nursing homes	~18,000	Universal CHG bathing plus nasal iodophor vs routine care	29% reduction in MDRO carriage 24% reduction in MRSA carriage 61% reduction in VRE carriage 52% reduction in ESBL carriage Primary trial results on infection and hospitalization: pending

[a] MDRO: multidrug-resistant organism; MRSA: meticillin-resistant Staphylococcus aureus; VRE: vancomycin-resistant enterococcus; ESBL: extended spectrum beta-lactamase producers.

Where should CHG be used? In what healthcare settings?

To date, clinical trials and other studies have repeatedly demonstrated the value of CHG bathing for infection prevention in healthcare settings where patients are vulnerable to infection. During hospitalization, this includes patients requiring intensive care and those with medical devices, both inside and outside of intensive care [49-51,53]. This benefit in the most vulnerable populations fuels hope for benefit in oncology and bone marrow transplant units, where data are yet sparse, but accruing [49,66]. Inpatient benefit further extends to surgical patients during the immediate peri-operative period, both before and after surgery [47].

Following discharge, CHG, in combination with nasal decolonization, has been shown to mitigate the high risk of infection and rehospitalization in MRSA carriers [54]. Similarly, evidence is growing for its benefit in reducing MDRO carriage and infection in long-term care settings [57,67]. This includes both long-term acute care hospitals and nursing homes where MDRO prevalence can be many-fold higher than in hospitals and patients have longstanding health issues that compound acute ones.

In outpatients, use should be commensurate to the vulnerability of infection. As an antiseptic, CHG has been used to mitigate the risk of infection due to chronic dermatologic conditions, as well as for secondary prevention in patients with recurrent *S. aureus* disease. However, vulnerability need not be for oneself, as CHG has been commonly and successfully used to decolonize healthcare workers who harbor MRSA in the setting of a healthcare-associated outbreak.

When should decolonization be used?

In healthcare settings, it is important to perform CHG bathing upon admission. Admitted patients feel unwell and may not have bathed for days. In addition, admission is a key moment where MDROs can be imported into a unit. Cleansing the skin is important for all these reasons and to reduce skin bioburden before surgery or placement of devices occur.

As to frequency of use, daily CHG bathing has been the most well studied, likely because daily bathing is routine in US ICUs where trials were performed, but also because CHG residue and reduced skin bioburden can last for up to 24 hours [27,43-45]. Thus, bathing daily could protect patients for the full duration of their hospital stay. Nevertheless, some evidence for MDRO and infection reduction with every other day bathing has emerged [64,68]. In addition, single or repeated use of a 5-day decolonization regimen in outpatients has been found to be successful [54,69].

Other considerations for use of decolonization include situations when treatment options are limited for a colonizing highly antibiotic resistant bacteria or a colonized patient is allergic to an extensive array of antibiotics. In these circum-stances, body decolonization as an infection prevention strategy can be life-saving, especially during periods of high vulnerability (e.g. hospitalization, operation, open wound, medical devices).

Table II

Top 10 pearls for appropriate chlorhexidine (CHG) bathing

Key Training Point	Details
1. Application and training matters	Nurses and nursing assistants are not inherently familiar with how best to clean non-intact skin, wounds and devices. Need directed training and need annual refresher training [70,71].
2. Not a topcoat	CHG is not to be applied after a bath; it is the bath itself. Apply with thorough massage to remove dirt, grime, and germs, and to allow CHG to bind to skin proteins and continue to kill germs for up to 24 hours.
3. Commonly missed areas	The neck is germ-ridden like the groin, but not as well cleaned. Other missed areas: back of knee, between fingers and toes [27].
4. Leave-on better than rinse-off	When possible, air dry rather than rinse off to retain germ-killing concentrations of CHG on the skin [43]. CHG only works after it dries (e.g. candidal rashes will improve with CHG application and drying, but if left moist in folds, CHG will not kill germs and moisture can worsen candidal rashes.)
5. Avoid cotton, use mesh sponge	Cotton binds CHG and limits its release to the skin [43]. For bed baths, use non-cotton cloths. For showering, a mesh sponge allows CHG to lather well and applies CHG well to skin.
6. Check compatibility	Contact manufacturers to ensure skin lotions and care products do not inactivate CHG.
7. Clean wounds and devices	Breaks in skin are entry points for germs to invade and cause infection. Clean wounds well unless large or deep, e.g. requires packing. Use a clean CHG cloth to clean the proximal 6 inches of all devices, including lines, tubes, and drains closest to the body, as well as over dressings. For patients who shower, devices are wrapped for waterproofing. After the shower, devices should be cleaned with a clean CHG cloth.
8. Clean the perineum	CHG is safe on vaginal epithelium. Thorough cleaning of the perineum was emphasized in several CHG clinical trials [50,52–54,56]. Cleaning with CHG reduces low-level bacteruria and funguria [74].
9. Clean the face	Clean face well due to common contamination from adjacent nose and mouth. Nose is the major reservoir for *S. aureus*. Avoid eyes and ear canal since CHG should not directly contact nerves (e.g. eyes, auditory nerves if tympanic membrane ruptured). Cleaning the face with CHG is emphasized in several clinical trials [52–54,56].
10. The nose matters for *Staphylococcus aureus*	Nasal decolonization is the workhorse for clearing *S. aureus*. CHG prevents spread, but does not clear carriage.

How should decolonization with CHG be performed?

Proper application of CHG is essential [70,71]. While, nurses and nursing assistants have personal experience bathing their own intact skin, it is unreasonable to assume that they would have inherent knowledge on how best to clean breaks in the skin, including abrasions, rashes, wounds, surgical incisions, and medical devices. In fact, the inherent response to these conditions is to avoid bathing those areas due to fear of causing pain. Nevertheless, those areas are portals of entry for infection that should be well cleaned to prevent infection. In fact, daily bathing coupled with the 24-hour germicidal benefit of CHG is most pertinent to those high risk skin areas to provide continued protection.

Several key training points in response to common errors are found in Table II. Of particular note is the recommendation to use CHG to clean the face, perineum, and all lines, tubes, drains, and other devices for at least 6 inches (15 centimeters) closest to the body. This was standard protocol and safely done for over one million baths in our collective trials. Our detailed protocols, videos, and educational materials are publicly available at several websites [63,72,73].

In addition to training staff, pre-launch activities should include ensuring that other topical products, such as lotions and barrier creams, are compatible with CHG. This is best done by contacting the manufacturer and exchanging incompatible or unknown products with those that will not inactivate CHG. In addition, it is important to note that CHG and bleach chemically interact in the laundry and produce brown stains. Thus, staff should avoid placing CHG saturated cloths directly onto sheets. Fortunately, once CHG is bound to the skin, it will not rub off onto sheets. While hospital laundry is often washed at a sufficiently high temperature to cause CHG to denature, on-site laundry temperatures in nursing homes or care homes is generally not able to prevent brown staining, and a switch from chlorine bleach to peroxide bleach is highly advisable if CHG is used in those settings. Finally, it is advisable to perform a skin check of patients prior to the launch of CHG bathing to avoid misattributing pre-existing skin issues to CHG when staff are unfamiliar with the product.

The adoption of CHG bathing should be considered a major campaign due to the importance of training, validation, and feedback. Training and re-training should be an annual competency for all staff performing bathing due to the importance of proper application. Assessing adherence is critical for success. Feedback about whether CHG bathing was performed and the quality of bathing enables correction and success. Simple skills assessment forms can be found online [75].

The spectre of resistance and future considerations

In an era where case reports of resistance occur shortly after each new antibiotic arrives on the market, it would be foolish to assume invincibility of any systemic or topical germicidal product. Nevertheless, there has been a hope that antiseptics would stave off resistance longer due to their small size and rapid bacteriocidal activity.

The natural diversity of CHG minimum inhibitory concentrations (MIC) (8 mg/mL for *S. aureus* and 32->300 mg/mL for Gram-negative bacteria) across wild-type bacteria raises the question about inherent mechanisms of resistance. In addition, efflux pumps have been identified that can expel CHG from bacteria. Clinically, two things have been noted. On one hand, elevations in CHG MIC have been reported to emerge while universal CHG bathing is being employed [76,77]. On the other hand, randomized clinical trials have not identified differential emergence of resistance associated with the decolonization group [49,50,54,78]. For MRSA, it may be that the combination of both CHG bathing and nasal decolonization reduces the emergence of resistance compared to CHG alone.

What is known is that applying 2% or 4% CHG products confers 20,000 mg/mL and 40,000 mg/mL of CHG to the skin, which is in far excess of bacterial MICs. Thus, proper application may be the key to not only achieving benefit, but also preventing resistance, especially if residual skin concentrations exceeding 500 mg/mL are maintained. Continued monitoring is clearly needed as the evidence-base accrues for the benefit of CHG bathing.

In the end, the spectre of resistance should not outweigh the value of CHG protocols in reducing MDRO transmission and infection, device-associated infections, and all-cause bacteremia. CHG bathing remains an astoundingly simple solution that has achieved some of the

largest proven gains in modern infection prevention. It should be applied as best practice to protect patients.

Of course, we should not become complacent. Science enables us to innovate and strive for improvement. If there are better alternatives or more effective strategies, we should press onward to find them. If resistance emerges, then necessity should drive the next invention. We must not be wedded to the best things of today, but always seek a future that will find us something more effective, lower in cost, and better able to protect humans from the persistent threat of infection.

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