Decolonization of Non-ICU Patients With Devices

Section 4 – Scientific Rationale

The Burden of Healthcare-Associated Infections

Healthcare-associated infections (HAIs) have been recognized as a major preventable cause of morbidity and mortality in the United States. In 1999, the Institute of Medicine (IOM) report "To Err Is Human: Building a Safer Health System" galvanized efforts to prevent healthcare-associated adverse events, including HAIs.[1] In 2002, it was estimated that over 1.7 million HAIs occurred annually in hospitals, resulting in 100,000 annual deaths at a cost of over $6.5 billion. The estimate is $40 billion for when out-of-hospital HAIs are included.[1] Since then, major efforts have been made at the national, State, and local level to reduce these preventable infections.[2]

In 2003, the IOM identified HAI prevention as a top 20 priority area for national action.[3] In 2008, the U.S. Government Accountability Office issued a report on HAIs in hospitals calling for national efforts by the Department of Health and Human Services (HHS) to prioritize prevention practices and standardize HAI surveillance.[4] In response, HHS spearheaded the development of the first National Action Plan to Prevent Healthcare-Associated Infections. In the meantime, The Joint Commission continued to increase its requirements for routine HAI surveillance for hospital accreditation,[5] and the Centers for Medicare & Medicaid Services (CMS) outlined and implemented a multiyear plan requiring hospitals to publicly report HAIs and perform well on HAI rankings or face reductions in reimbursement.[6]

Currently over 22,000 hospitals and other healthcare facilities report HAI events through the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) system. [2-7] In addition to providing gold-standard criteria for identifying HAIs, the NHSN has become the national repository for acute-care and long-term care facilities to report HAI surveillance data. Through use of NHSN data, CMS and State health departments are generating public reports of hospital-specific HAI performance. HAI performance has been adopted as a core safety measure by many state regulatory agencies, CMS, and private accrediting bodies such as The Joint Commission and Leapfrog.

Interest in Broad-Based HAI Reduction Strategies

The focus on HAIs produced important developments and raised important questions about prevention. It led to national programs and targeted strategies to reduce device and procedure-related HAIs, such as central-line–associated bloodstream infection (CLABSI), catheter-associated urinary tract infections (CAUTI), and surgical site infections (SSI), as well as targeted efforts to reduce multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE). However, as pressure mounted to reduce all nationally monitored HAIs, interest increased in broad-based strategies that could be applied to a wide range of hospitalized patients to prevent multiple HAIs at the same time. The appeal in broad-based strategies was driven by the strong desire to protect patients from several types of HAIs, the limited capacity for multiple infection

prevention campaigns by infection prevention programs, and the need for labor-efficient and cost-effective strategies.

Decolonization as a Broad-Based Strategy

Most HAIs are caused by bacteria that reside on the skin and in the nose and gain access to the bloodstream, lungs, and bladder by way of invasive devices and incisions that breach normal host defenses. These infecting bacteria may be the patient's normal flora, or they may be new, often antimicrobial-resistant organisms acquired during hospitalization. Reducing the bacterial burden through topical decolonization of the skin and nasal reservoirs has proven to be an effective broad-based strategy to reduce a wide range of HAIs.

Decolonization procedures have evolved and now most commonly involve the use of chlorhexidine gluconate (CHG) topical antiseptic for bathing or showering, with or without nasal decolonization using mupirocin antibiotic ointment or povidone iodine (iodophor). CHG has been used in healthcare for over 60 years and is FDA cleared for cleansing the skin and wounds. When applied well, particularly as a 2 percent no-rinse bathing solution, CHG is absorbed onto the skin surface and has up to 24 hours of persistent germicidal activity on the skin,[8] allowing continuous protection in the hospital with the use of daily bathing. Mupirocin nasal antibiotic ointment was FDA approved in 2002 and has been shown in clinical trials to reduce colonization and infection due to *S. aureus*, which resides most commonly in the nose. [9-12] Together, these topical products have proven effective for preventing HAIs when universally provided to high-risk groups, such as those undergoing surgical procedures, or those requiring ICU care.

The increased appreciation of HAI impact on morbidity and mortality stimulated the conduct of large-scale randomized clinical trials to evaluate decolonization and other infection prevention strategies. Large-scale pragmatic randomized trials involving CHG with and without nasal decolonization are reviewed and summarized in Table 4-1.[13]

Table 4-1. Large-Scale Randomized Clinical Trials Evaluating CHG Decolonization To Reduce HAIs

Location	Trial and Target Population	N	Intervention	Impact of Decolonization
Preoperative Use	***Bode et al.***[14]	918	Universal inpatient screening for *S. aureus* carriers randomized to CHG and mupirocin versus routine care	Among *S. aureus* carriers, 58% less inpatient *S. aureus* infection, including 79% less deep surgical site infection
	Harbarth et al.[15]	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 (ICU)	***Climo et al.*** 6 academic medical centers[16]	7,727	Universal CHG bathing versus routine care (as-treated analysis)	23% less MRSA/VRE acquisition 28% less bloodstream infections 53% less CLABSI
	REDUCE MRSA Trial 43 community hospitals[12]	74,256	Group A: Targeted CHG and mupirocin for MRSA carriers Group B: Universal CHG and mupirocin Group C: Routine care	Group B: 37% less MRSA positive clinical cultures 44% less bloodstream infections
	Pediatric SCRUB Trial[17] 5 academic medical centers	4,947	Universal CHG bathing versus routine care (as treated analysis)	33% less bloodstream infections 30% less CLABSI
	Mupirocin Iodophor Swap Out 137 community hospitals[18]	~250,000	Group A: Universal CHG and mupirocin Group B: Universal CHG and iodophor	Group A: 18% less *S. aureus* positive clinical cultures 14% less MRSA positive clinical cultures Equivalent to Group B for bloodstream infections

Location	Trial and Target Population	N	Intervention	Impact of Decolonization
Non-ICUs	***ABATE Infection Trial*** 53 community hospitals[19]	339,902	Universal CHG bathing plus targeted mupirocin for MRSA carriers versus routine care	No difference in MRSA/VRE clinical cultures or bloodstream infection in overall non-ICU population, but in subset with medical devices: 37% less MRSA/VRE positive clinical cultures 32% less bloodstream infections (post-hoc analysis)
Postdischarge	***CLEAR Trial***[20]	2,121	Targeted education plus 5 days of CHG bathing, CHG mouthwash, and mupirocin repeated twice a month for 6 months versus education alone for MRSA carriers	In the year following discharge: 30% less MRSA infection 17% less all-cause infection Reduced readmissions
Nursing Homes	***Bellini et al.***[21]	4,750	Universal screening for MRSA followed by targeted CHG bathing, CHG mouthwash, nasal mupirocin, and room disinfection for MRSA carriers versus routine care	No difference in one-day MRSA point prevalence
	Protect Trial 28 nursing homes[22,23]	~18,000	Universal CHG bathing plus nasal iodophor versus routine care	18% fewer hospital transfers due to infection 23% fewer discharges to a hospital 29% reduction in MDRO carriage 24% reduction in MRSA carriage 61% reduction in VRE carriage 52% reduction in ESBL carriage

Huang SS. Chlorhexidine-based decolonization to reduce healthcare-associated infections and multidrug-resistant organisms (MDROs): who, what, where, when, and why? J Hosp Infect. 2019 Nov;103(3):235-43. Adapted with permission.

CHG = chlorhexidine gluconate; ESBL = extended spectrum beta-lactamase producers; MDRO = multidrug-resistant organism; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococcus

The results consistently show that decolonization in the ICU setting results in significant decrease in HAIs and colonization by MRSA and MDROs. In other care settings, the results are dependent on the specific care context. For example, in non-ICU patients, the **A**ctive **Bat**hing to **E**liminate Infection (ABATE Infection) Trial found that CHG decolonization had an impact primarily in the subset of patients with specific invasive devices: central lines, midlines, and lumbar drains.

HAIs Targeted by Decolonization

Decolonization has been broadly studied for its impact on MRSA infection, bloodstream infections including central line-associated bloodstream infections (CLABSI), and SSIs. We briefly review the importance of MRSA and CLABSI as a prelude to introducing this toolkit in the context of a prior AHRQ ICU decolonization toolkit.

Importance of MRSA in HAI Prevention

S. aureus is a major pathogen associated with HAIs, given its virulence, prevalence, diversity of disease spectrum, and propensity for widespread transmission. *S. aureus* caused 120,000 bloodstream infections and 20,000 deaths in the United States in 2017.[24] MRSA is a form of *S. aureus,* which is specifically resistant to oxacillin and similar antibiotics. MRSA is well known for producing HAIs, including skin and soft tissue infections, pneumonia, surgical site infections, blood and urine infections, and sepsis.[25-30] In 2000, MRSA was reported to cause or complicate 278,000 U.S. hospitalizations annually, resulting in 56,000 septic events and 19,000 deaths.[28] While prevention efforts have reduced MRSA HAIs, gains have plateaued in recent years and MRSA remains a major source of preventable morbidity and mortality associated with healthcare facilities.[24,25,31] This toolkit will describe a proven decolonization strategy to reduce MRSA and VRE in adult non-ICU patients with selected medical devices.

Importance of Bloodstream Infections in HAI Prevention, Including CLABSI Events

There has been a longstanding need to prevent device and procedure-associated infections. The breach of skin integrity by medical devices and surgeries compromises one of the most important human organs that protects against infection. While CLABSI rates have declined by over 50 percent in the past two decades, they remain a major source of serious bloodstream infections. Concurrently, the use of invasive devices has risen substantially, and now nearly 20 percent of hospitalized patients have a central line on any given day.[32] Despite gains in preventing CLABSI, there were an estimated 18,000 CLABSI cases in ICU patients and an additional 23,000 CLABSI cases in non-ICU patients in 2009.[33] Decolonization has been recommended in the Society for Healthcare Epidemiology of America (SHEA) Compendium as a 1A evidence-based strategy for CLABSI prevention in ICUs due to several clinical trials showing benefit to bloodstream infections and CLABSI, in particular[34] (Table 1). This toolkit will describe a proven decolonization strategy to reduce bloodstream infections in adult non-ICU patients with selected medical devices.

Effectiveness of Decolonization With Chlorhexidine and Mupirocin

The use of decolonization to prevent HAI has biological plausibility. CHG and similar compounds reduce bacteria on the skin to prevent infection. This reduction in bioburden reduces the likelihood of infection from a patient's own flora, and it also reduces the spread of pathogens from one patient to another. Large-scale randomized clinical trials have now informed best practice guidance on patient populations that may benefit from decolonization.

CHG has been safely used for bathing, showering, and dental hygiene for over 60 years. It is used for showering as a 4 percent rinse-off solution or for bathing as a 2 percent no-rinse solution that is directly applied to skin as an antiseptic skin cleanser. Numerous studies have shown marked reductions in skin bacteria following serial CHG bathing or showering,[35-41] and it is widely used as a preoperative showering agent.[42,43] CHG is absorbed onto the skin surface for up to 24 hours after application and retains its antibacterial activity.

Evidence supports repeated application for sufficient and persistent skin decontamination. [38-41,44] In addition, CHG bathing as a universal strategy has gained favor since evidence is mounting that CHG can reduce colonization and infection from a variety of HAI pathogens[45-47] with a 44–87 percent reduction in bloodstream infection in ICU patients.[46,47,48,49,51] There is also evidence that CHG skin bathing reduces MRSA acquisition and infection by 40–50 percent in high-risk settings such as ICUs.[12,46,49-51]

Mupirocin is a prescription topical drug that is FDA approved for eradicating nasal carriage of *S. aureus*, including MRSA. Nasal mupirocin is highly effective in eradicating *S. aureus* in the short term. Several studies have shown 90 percent efficacy within two weeks of a 5-day regimen.[52-56] The impact of nasal decolonization is substantial, as it also significantly reduces short-term hospital-associated MRSA transmission and infections by over 50 percent in observational and crossover intervention studies.[49,52,57,58,59] However, long-term clearance after a single treatment regimen is only 60 percent after 6–8 weeks, largely due to recolonization with a person's original strain. [11,49,53-56,60-62] Therefore, repeated courses may be necessary.

Used together, CHG and mupirocin provide effective decolonization support for a range of important HAI pathogens. In the following section, we review evidence for their joint use in ICUs as a prelude to discussing the value of their use in adult non-ICU patients who have medical devices.

Precedent in ICU Patients: The ICU Decolonization Toolkit From The REDUCE MRSA Trial

This non-ICU decolonization toolkit has precedent in a previously released ICU toolkit for universal decolonization (https://www.ahrq.gov/hai/universal-icu-decolonization/index.html). In 2013, three large cluster-randomized clinical trials were published, which evaluated universal ICU decolonization with and without nasal decolonization (Table 1).[12,16,17] The AHRQ-funded **R**andomized **E**valuation of **D**ecolonization versus **U**niversal **C**learance to **E**liminate MRSA (REDUCE MRSA) Trial was the largest of the three trials and involved nearly 75,000 adult ICU patients in 43 community hospitals (across 16 States) affiliated with HCA Healthcare (formerly Hospital Corporation of America).[14] The hospitals were randomized to one of three study groups:

Group 1, Routine Screening and Isolation: Continued bilateral nares screening on ICU admission, with routine use of contact precautions for patients known to be MRSA carriers by history, screening test, or clinical cultures.

Group 2, Targeted Decolonization: MRSA screening and routine contact precautions similar to Group 1. In addition, ICU patients known to be MRSA carriers received 5 days of twice daily mupirocin and 5 daily baths with no-rinse 2 percent CHG cloths.

Group 3, Universal Decolonization: MRSA screening was discontinued. Routine contact precautions continued to occur for known MRSA carriers by history or clinical cultures. In addition, all ICU patients received 5 days of twice daily mupirocin and daily bathing with no-rinse 2 percent CHG cloths for the duration of the ICU stay.

The REDUCE MRSA Trial found that Universal Decolonization was most successful in reducing the trial outcomes of MRSA-positive clinical cultures and bloodstream infections attributable to the ICU. Compared with the control arm (Group 1), Universal Decolonization Group patients experienced a statistically significant 37 percent reduction in MRSA-positive clinical cultures and a statistically significant 44 percent reduction in all-cause bloodstream infections, including CLABSIs.[12]

The success of the REDUCE MRSA Trial led to the creation of the AHRQ Universal Decolonization Toolkit (https://www.ahrq.gov/hai/universal-icu-decolonization/index.html), which provided a roadmap for hospital infection prevention or quality improvement programs to evaluate their need and readiness to implement universal decolonization in their ICUs. The toolkit provided the protocols and training materials to implement the universal decolonization intervention of the REDUCE MRSA Trial.

This current toolkit extends the application of CHG and mupirocin to hospitalized patients with selected medical devices outside of the ICU based upon the ABATE Infection Trial (see below).[2] Elements of the Targeted Decolonization toolkit will be familiar to hospitals that have already implemented universal ICU decolonization with CHG and mupirocin. If an ICU universal decolonization strategy has not yet been implemented, we recommend considering concurrent or sequential implementation of decolonization in that population (described at: https://www.ahrq.gov/hai/universal-icu-decolonization/index.html) because the rates of hospital-associated bloodstream infections and MRSA clinical cultures are known to be higher in ICU patients. Thus, such benefits may be greater for the ICU subpopulation. Additional reasons relate to logistics. Universal strategies are generally easier to implement than targeted strategies that require methods for identifying qualifying patients and ensuring a different process of care for those patients. Developing experience with whole-unit practices for ensuring adequate supplies and staff training can help with the transition to a practice that involves targeted criteria for only some patients in a unit. Finally, non-ICU bathing strategies require additional training for addressing questions from patients who are alert or desire self-bathing or showering instructions.

Rationale for Evaluating Decolonization To Reduce HAI Beyond Intensive Care Units

For over 30 years, the major focus of HAI prevention has been on ICUs because of the combination of high complexity medical care, high prevalence of invasive interventions, and severity of illness result in ICU patients having the highest risks for HAIs.[45,46,49,63-68] Numerous studies have described the morbidity and mortality attributable to this setting and demonstrated gains in reducing catheter-related bloodstream infections,[45,46, 65,69] catheter-related urinary tract infections, and pneumonia [70-73] in ICU settings.

Although ICUs have the highest *incidence* rate of HAIs, the vast majority of HAIs, in absolute numbers, actually occur in non-ICU settings (i.e., non-ICU settings have a higher attributable fraction of HAIs). This has prompted attention on HAIs occurring outside of ICUs. Non-ICU settings most commonly consist of step-down units, which represent an intermediate level of care between the ICU and a routine non-ICU area, as well as medical, surgical, mixed medical/surgical, and oncology units. It is estimated that 75 percent of HAIs occur outside of ICU settings.[26]

The ABATE Infection Trial was the first large-scale cluster-randomized trial of decolonization in the non-ICU setting. This trial was important because a decolonization strategy that works in ICUs may not be effective in non-ICU settings. There are several reasons for this. First, HAI rates in non-ICUs are generally lower than rates found in ICUs. Use of invasive devices is less frequent in non-ICU settings, and reducing bacterial reservoirs on the skin and in the nose may convey a smaller benefit. Nevertheless, the relatively larger numbers of non-ICU patients can mean that the total number of HAIs may be similar or greater in non-ICU settings.

Second, a non-ICU decolonization regimen cannot be delivered in an identical fashion to the ICU setting. Patients in non-ICU settings are typically more awake, are more ambulatory, and some may refuse a daily bath or choose to perform their own bed bath. Others may choose to shower, where rinsing off CHG leaves less residual effect on the skin compared with a no-rinse bed bath. Thus, decolonization will be generally more difficult to standardize and apply uniformly and effectively outside of the ICU. Nevertheless, this is an important aspect of real-life circumstances in non-ICU settings.

Third, the level and intensity of contact between patients and nursing staff differs between ICU and non-ICU settings. It also differs between patients themselves, especially those sharing a room in general hospital units. Since these interactions are important determinants of transmission of pathogens to patients, the results of an ICU intervention are not necessarily applicable to the non-ICU setting. Thus, it was important to test the effectiveness of a decolonization regimen under conditions of actual use and assess both its impact on infections and the frequency of adverse effects on patients. This was done through the ABATE Infection Trial.

The ABATE Infection Trial

The ABATE Infection Trial was a large-scale cluster randomized trial of 53 community hospitals located in 14 states affiliated with HCA Healthcare that evaluated the impact of universal CHG bathing for adult non-ICU patients and additional nasal decolonization for MRSA carriers on the

outcomes of MRSA-positive and VRE-positive clinical cultures and all-cause bloodstream infections. We define MRSA carriers as patients known to the hospital to be MRSA carriers (by reported history, prior culture result, or information from transferring facilities).

Participating hospitals were randomized to one of two arms of the ABATE Infection Trial:

> **1. Routine Bathing:** Continued use of routine nonantiseptic disposable cloths for bed bathing, and liquid soap for showering at usual frequency
>
> **2. Decolonization:** Universal daily bathing with 2 percent leave-on CHG-impregnated cloths for baths **or** 4 percent rinse-off CHG for showering for the duration of the non-ICU stay plus targeted nasal mupirocin for MRSA carriers for 5 days. The bathing protocol involved cleaning the 6 inches of all devices closest to the patient.

The ABATE Infection Trial involved nearly 340,000 patients in 194 adult non-ICUs. It found that universal CHG bathing for all patients outside the ICU plus mupirocin for MRSA carriers did not significantly reduce clinical cultures with multidrug-resistant organisms or all-cause bloodstream infections compared with routine care. However, **a significant benefit was found in the subgroup of patients with any of the three medical devices that were electronically trackable (i.e., central lines (including dialysis catheters and port-a-caths), midline catheters, and lumbar drains). In these patients, decolonization with CHG decreased all-cause bacteremia by 32 percent and MRSA-positive and VRE-positive clinical cultures by 37 percent.** This reduction is even more meaningful considering patients with medical devices represented only 10 percent of the total study population but were responsible for 37 percent of MRSA-positive and VRE-positive cultures and 56 percent of all-cause bloodstream infections.

The materials provided in this toolkit reflect the protocols and training materials from the ABATE Infection Trial and focus on the devices studied in the ABATE Infection trial, specifically central lines, midline catheters, and lumbar drains. Data were available to trial investigators for only these three devices. Thus, the impact of non-ICU decolonization on other medical devices in the ABATE Infection Trial is unknown. Among the three devices, the estimated benefit of decolonization on each specific device was the same. In this toolkit, we refer to these devices as "selected medical devices," in reference to devices that were studied within the ABATE Infection Trial.

This toolkit does not preclude the use of its decolonization protocol in patients with other devices (e.g., urinary catheters), but such use would be based upon pragmatic needs or literature evidence other than from the ABATE Infection trial.[74] For example, secondary analysis of the REDUCE MRSA Trial, showed a reduction in bacteriuria and candiduria in male ICU patients who received decolonization.[74]

Safety of Mupirocin and Chlorhexidine

Both mupirocin and CHG have excellent safety profiles. Systemic absorption of both drugs is minimal.[75-79] Of the minimal amount of mupirocin that is absorbed, nearly all is rapidly converted to monic acid, an inactive metabolite.[75,76] Furthermore, systemic absorption remains negligible following single or repeated intranasal applications over consecutive days in adults.[47] Multiple observational studies and randomized controlled trials have also shown no systemic

absorption of mupirocin following intranasal application.[78-82] Safety data for mupirocin from the manufacturer states that fewer than 1 percent of patients in clinical trials withdrew due to adverse events. The most frequently reported adverse events were as follows: rhinitis (1.0%), taste perversion (0.8%), and pharyngitis (0.5%). Postmarketing surveillance has not identified any additional concerns.

As an over-the-counter skin cleanser used in healthcare for over 60 years, CHG has an even more extensive safety record.[46,50,58,59,83-89] Several groups have confirmed the absence of systemic absorption following topical use or oral rinsing with CHG.[90-93] Moreover, even if ingested, CHG is known to have negligible absorption with undetectable blood levels.[94-96] Side effects are largely limited to skin irritation, which is uncommon, and anaphylaxis, which is extremely rare. In fact, anaphylaxis has only been reported in case reports.[97,98] Estimates for these effects are expected to be very small given the large numbers of people using an unregulated over-the-counter product. No deleterious effects have been reported with daily use in either long-term ICU patients or with repeated use in the post-discharge setting.[20,48,49] The major manufacturer of over-the-counter CHG states that CHG "can be used many times a day without causing irritation, dryness, or discomfort."[98] It is also safe to use on superficial wounds. CHG is currently cleared by the U.S. Food and Drug Administration (FDA) for use in patients at least 2 months of age. Notably, in 2012, the FDA changed the recommendation for CHG use in neonates less than 2 months of age from "contraindicated" to "use with care." This toolkit is specifically designed for adults in noncritical care units who have selected medical devices.

Nasal Iodophor as an Alternative to Mupirocin

Due to U.S. regional differences in mupirocin resistance[99] and facility preferences for mupirocin versus nasal iodophor for nasal decolonization protocols (e.g., pre-operative decolonization), this toolkit will provide pragmatic directions for the use of nasal iodophor as an alternative to mupirocin.[100] Hospital choices may be further informed by the Mupirocin-Iodophor ICU Decolonization Swap Out Trial, a large-scale non-inferiority pragmatic cluster-randomized trial comparing decolonization with mupirocin/CHG to iodophor/CHG in ICU patients.[18]

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