Intensive Care Med (2015) 41:1351–1354
DOI 10.1007/s00134-015-3846-6

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Understanding chlorhexidine decolonization strategies

Received: 31 March 2015
Accepted: 24 April 2015
Published online: 19 June 2015

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An estimated 4.5 % of acute care hospital stays are complicated by a health care-associated infection (HAI) making infection the most common complication among hospitalized patients. Critically ill patients are at greatest risk for HAIs, and these infections are associated with worse outcomes including increased morbidity, higher rates of death [1] and increased health care costs [2]. To reduce the incidence of HAIs, numerous interventions aimed at decreasing nosocomial transmission of pathogens are advocated, such as hand hygiene and isolation of patients infected or colonized with multidrug-resistant organisms (MDROs). Alternative approaches focus not on transmission of pathogens but rather on limiting reservoirs of potential pathogens on the skin, in the mouth, and gut of patients. Patients may bring these organisms with them to the hospital or become colonized after admission. Decolonization strategies target microbial reservoirs with antimicrobials, often using the broad-spectrum, topical, antimicrobial agent chlorhexidine. Here, we discuss the use of chlorhexidine for the decolonization of the mouth and skin of critically ill patients.

Translocation of oropharyngeal flora or nosocomial pathogens into the lower respiratory tract is believed to be the main contributor to the development of ventilator-associated pneumonia. Consequently, attempted decolonization of the mouth of ventilated patients with chlorhexidine rinses or swabs is performed in many ICUs [3]. However, as recently reviewed, numerous, generally small, trials of this intervention have yielded inconsistent results [4]. When examining studies of mechanically ventilated patients only, decolonization did not result in a statistically significant reduction in nosocomial pneumonia or duration of mechanical ventilation. By contrast, in studies of cardiac surgery patients (where oropharyngeal decolonization is done for all patients) chlorhexidine reduces risk of lower respiratory tract infection. Although possibly beneficial, decolonization may not be benign, with recent reports suggesting that aspiration of oral antiseptics (povidone-iodine) by ventilated patients may lead to acute respiratory distress syndrome [5].

Patients' skin harbors numerous microorganisms and invasion by these organisms is thought to be a mechanism contributing to certain HAIs, including central line-associated bloodstream infections (CLABSI). Bathing patients with solutions containing chlorhexidine reduces the number of bacteria on the skin [6], which has prompted some to adopt the practice for hospitalized patients at highest risk for HAIs. This intervention, alone or as part of a bundled approach, has been the subject of multiple quasi-experimental studies that use variations of a sequential (pre-, post-intervention) design. Although these studies have reported a variety of beneficial effects,

the interpretation of all such studies is limited by the potential for bias from intentional or unmeasured co-interventions, and changes to practice over time [7, 8].

Over the past several years, three large, cluster-randomized trials of chlorhexidine bathing have been reported as well as a fourth study that included chlorhexidine bathing as a component of multiple interventions. As summarized in Table 1, Climo et al. [9] conducted a multicenter, cluster-randomized, cross-over trial of daily chlorhexidine bathing in 7727 adult patients. The study demonstrated significant reductions in the rates of MDRO acquisition (new colonization with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci) and hospital-acquired bloodstream infections during periods of chlorhexidine bathing. The reduction in hospital-acquired bloodstream infections was largely driven by decreased blood cultures positive for the skin commensal coagulase-negative staphylococci, raising the possibility that chlorhexidine may have reduced the incidence of blood culture contamination rather than true infection. Milstone et al. [10] investigated the effect of chlorhexidine bathing in a pediatric population with a multicenter, cluster-randomized, cross-over trial of 4947 critically ill children. The intention to treat analysis did not reveal a significant reduction in the primary outcome of rates of bacteremia during chlorhexidine bathing. When the analysis was limited to only patients that received the intervention (per protocol analysis), a

Table 1 Summary of studies on chlorhexidine bathing

	Climo [9]	Milstone [10]	Huang [11]	Noto [12]
Design	Cluster-randomized	Cluster-randomized	Cluster-randomized	Cluster-randomized
Setting	Multicenter 9 ICUs	Multicenter 10 ICUs	Multicenter 74 ICUs	Single center 5 ICUs
No. patients	7727 adults	4947 children	74,256 adults	9430 adults
Intervention	2 % chlorhexidine washcloths	2 % chlorhexidine washcloths	1. Screening and isolation	2 % chlorhexidine washcloths
Control	Non-antimicrobial washcloths	Non-antimicrobial washcloths or soap and water	2. Screening and selective decolonization[a] 3. Universal decolonization[a]	Non-antimicrobial washcloths
Duration of intervention	6 months	6 months	18 months	10 weeks
Cross-over	Yes, single	Yes, single	No	Yes, multiple
Primary outcome	MDRO acquisition HA-BSI	Bacteremia	MRSA-positive clinical cultures	Composite rate of CLABSI, CAUTI, VAP, *C. difficile*
MDRO acquisition	5.1 and 6.6 per 1000 patient-days in chlorhexidine and control ($P = 0.03$)	Not assessed	Not assessed	Not assessed
Bloodstream infections	HA-BSI 4.78 and 6.6 per 1000 patient-days in chlorhexidine and control ($P = 0.007$)	All BSI 3.52 and 4.93 per 1000 patient-days in chlorhexidine and control ($P = 0.199$)	Significant reduction in HA-BSI with universal decolonization	HA-BSI 5.00 and 5.45 per 1000 patient-days in chlorhexidine and control ($P = 0.53$)
Blood culture contamination	Not assessed	Not assessed	Not assessed	4.84 and 5.45 per 1000 patient-days in chlorhexidine and control ($P = 0.40$)
Other outcomes	Significant reduction in CLABSI	Non-significant reduction in CLABSI	Significant reduction in MRSA clinical cultures with universal decolonization	No significant difference in rates of VAP, CLABSI, CAUTI, or clinical cultures positive for MDROs

MDRO multidrug-resistant organisms, *HA-BSI* hospital-acquired bloodstream infection, *CLABSI* central line-associated bloodstream infection, *CAUTI* catheter-associated urinary tract infection, *VAP* ventilator-associated pneumonia, *BSI* bloodstream infection, *MRSA* methicillin-resistant *Staphylococcus aureus*

[a] Decolonization included chlorhexidine bathing and nasal mupirocin

significant reduction in bacteremia was observed in the chlorhexidine group, with the largest reduction in the subset of blood cultures positive for coagulase-negative staphylococci. A large, cluster-randomized study of targeted versus universal decolonization demonstrated a reduction in total bloodstream infections in the universal decolonization arm [11]. Like the two studies above, this outcome was also driven largely by a reduction in blood cultures positive for skin commensal organisms. This decolonization intervention included both nasal mupirocin as well as chlorhexidine bathing; therefore the individual contribution of chlorhexidine bathing cannot be determined. In contrast to these findings, we recently published a single-center, cluster-randomized, multiple cross-over trial of chlorhexidine bathing of 9340 adults [12]. The intervention and control treatments were similar to those of Climo but we found no difference between treatment groups in the rates of the primary outcome, a composite of CLABSI, catheter-associated urinary tract infections, *Clostridium difficile* infection, and ventilator-associated pneumonia. Rates of hospital-acquired bloodstream infections and blood culture contamination also did not differ between groups.

The available evidence supporting chlorhexidine-based oropharyngeal decolonization to prevent lower respiratory tract infections suggests a small benefit but is inconclusive. Chlorhexidine bathing to decolonize patients' skin consistently reduces colonization by MDROs and may reduce the incidence of hospital-acquired bloodstream infections, particularly those caused by skin commensal organisms, some of which are likely the result of blood culture contamination. These findings, however, were not reproduced in a large trial of chlorhexidine bathing, suggesting that this practice is not universally beneficial to patients or effective in all settings. These strategies expose a large population of patients to chlorhexidine, the overwhelming majority of which will never experience an HAI. Although reductions in blood culture contamination may be beneficial, these could be attained through interventions targeting only the subset of patients that have blood cultured. Furthermore, adverse or allergic reactions to chlorhexidine are rare, but serious reactions have been reported [13]. In addition, aspiration of chlorhexidine causes lung injury in preclinical studies [14]. Decolonization strategies using chlorhexidine are associated with infections caused by organisms with reduced susceptibility to chlorhexidine [15, 16], raising concern for the development of chlorhexidine resistance that could limit its utility in perioperative and periprocedural settings. It is unknown if chlorhexidine selects for cross-resistance to other antibiotics or disinfectants. In a recent study, chlorhexidine bathing did not reduce colonization or infections caused by drug-resistant Gram-negative organisms, suggesting it has limited utility for this group of nosocomial pathogens [17]. Disruption of the microbiome has been associated with numerous disease states in recent years and the consequences of decolonization on the microbiome and disease are unknown. Finally, chlorhexidine-based decolonization strategies increase costs, utilizing limited health care resources. In conclusion, although chlorhexidine-based decolonization may be of benefit in select situations and should remain in the armamentarium of strategies to prevent HAIs, universal implementation of these practices warrants caution and further consideration in light of the available evidence and potential for harm.

Conflicts of interest The authors declare no conflicts of interest.

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