Nasal Iodophor Antiseptic vs Nasal Mupirocin Antibiotic in the Setting of Chlorhexidine Bathing to Prevent Infections in Adult ICUS: A Randomized Clinical Trial

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Mupirocin-Iodophor Swap Out Trial
Statistical Analysis Plan

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Background

Universal decolonization of all adult ICU patients with daily chlorhexidine (CHG) baths is widely implemented as ICU standard of care with and without nasal mupirocin due to several trials including the REDUCE MRSA Trial. This 43-hospitals trial showed a relative 37% reduction in ICU-associated methicillin resistant *S. aureus* (MRSA) clinical cultures and a relative 44% reduction in all-cause bloodstream infections.

Combined use of CHG with mupirocin is driven by the fact that *Staphylococcus aureus* is a common community and healthcare-associated pathogen responsible for disease in ICU settings. Nevertheless, the variability in mupirocin resistance in various geographic areas (near zero to >15%) has led intensivists to be circumspect in whether they implement universal CHG bathing alone or with universal mupirocin. While the majority of MRSA are still susceptible to mupirocin, the concern about whether mupirocin resistance will continue to rise has led to interest in finding alternative effective agents.

For this reason, the Mupirocin-Iodophor Swap Out Trial was undertaken as a cluster randomized non-inferiority trial in 137 HCA Healthcare hospitals with hospitals randomized to:

Arm 1: Mupirocin-CHG (Usual Care)
Hospitals will continue daily bathing with chlorhexidine plus twice daily intranasal application of mupirocin ointment upon admission to all ICUs and continuing for 5 days or until discharge from the ICU.

Arm 2: Iodophor-CHG
Hospitals will continue daily bathing with chlorhexidine, but switch from mupirocin to twice daily intranasal application of 10% povidone-iodine (iodophor).

Trial Outcomes

Trial outcomes are found in the below table.

Mupirocin-Iodophor Swap Out Trial Outcomes

Outcome	Metric
Primary Trial Outcome	ICU-attributable *S. aureus* clinical cultures (MRSA + MSSA)
Secondary Trial Outcomes (primary manuscript)	ICU-attributable MRSA clinical cultures ICU-attributable all-cause bloodstream infection
Other pre-specified secondary exploratory analyses for later manuscripts	Mupirocin and iodophor resistance in MRSA isolates

Analysis

The primary analysis will be an as-randomized proportional hazards model to evaluate for non-inferiority at a margin of 10% (difference in relative hazard). Model terms will include arm, period (baseline vs. intervention) and an arm by period interaction term to assess whether the difference in relative hazard between the baseline and intervention period differs significantly between the two arms. Clustering within hospital will be accounted for using shared frailties, i.e., a random intercept for each hospital, and, if it should become technologically feasible, an additional random intercept for each ICU within hospital and for repeated hospital stays for each person.

- Null hypothesis (H_0): the change in relative hazard of clinical culture of *S. aureus* in the Iodophor-CHG arm is higher than (inferior to) the change in the Mupirocin-CHG arm by more than 10%
- Alternative hypothesis (H_1): the change in relative hazard of clinical culture of *S. aureus* in the Iodophor-CHG arm is higher than (inferior to) the Mupirocin-CHG arm by 10% or less

Phase-in period data will not be included in the analysis.

To be explicit, the primary analysis will take the form of $\lambda_{ij}(t) = \lambda_0(t)e^{\beta_1 Arm_{ij}+\beta_2 Per_{ij}+\beta_3 Arm_{ij}*Per_{ij}+\gamma_i}$ where $\lambda_{ij}(t)$ is the time t of the *S. aureus* clinical culture for person j at hospital i. The baseline hazard function for time t, $\lambda_0(t)$, is shared by all people; $\gamma_i$is the frailty shared by patients at hospital i. The linear predictor in the exponent functions as in a linear model, where Arm_{ij} indicates the treatment arm of person j in hospital i is the iodophor arm, and Per_{ij} indicates that person j in hospital i was seen in the intervention period. Thus β_3 is the estimated differential effect of iodophor relative to mupirocin in the intervention period compared to baseline. While software is currently not able to include frailties for multiple visits per person or for multiple ICUs per hospital or for multiple periods per hospital on the scale of the data, we will include them if this should become possible by the time the trial is analyzed.

The primary outcome of the trial is ICU-attributable *S. aureus* clinical cultures (MRSA + MSSA) where ICU-attributable is defined as *S. aureus* cultures occurring in specimens collected from study cohort patients from the 3rd day of an ICU stay through 2 days after ICU discharge. This outcome will be assessed using an as-randomized unadjusted proportional hazards model as described above with two-sided significance set at alpha = 0.05, consistent with FDA standards of non-inferiority (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials). The pre-specified non-inferiority margin, we repeat, is 10%.

There is reason to suspect that nasal iodophor may be inferior to mupirocin due to FDA clearance based upon suppression versus cidal kill for *S. aureus*, which is the reason for the non-inferiority trial. However, conversely, if iodophor is found to be non-inferior, we are declaring the a priori intent to assess for superiority because of evidence of mupirocin-resistant *S. aureus* strains where none is expected to exist for iodophor. For this reason, if iodophor is found to be non-inferior in the primary outcome of the trial, we will also report the pre-specified assessment of superiority which is already performed in the primary analysis.

Secondary non-inferiority outcomes include 1) ICU-attributable MRSA clinical cultures and 2) ICU-attributable all-cause bloodstream infection. These will be assessed using an as-randomized unadjusted proportional hazards model as described above. We will use two-sided significance tests set at alpha = 0.05 for each outcome to determine possible inferiority with greatest possible sensitivity, again with a non-inferiority margin of 10%. Due to the above antibiotic-resistance rationale to suspect possible superiority, if non-inferiority is met for these secondary outcomes, we will perform a pre-specified assessment of superiority at a two-tailed significance set at alpha = 0.025, which accounts for the multiple comparisons of two outcomes. To be clear, the non-inferiority tests are not adjusted for multiple testing, while the superiority tests, if they are performed, will be adjusted for multiple testing, for conservatism.

Additional analyses will include as-treated and adjusted models, which will be reported as point estimates with confidence intervals without p-values. The reason for including these analyses is to provide additional information related to the trial outcomes for reader assessment of potential confounders. The reason to not include them in a formal multiple comparisons adjustment is because these analyses are non-independent evaluations related to the as-randomized unadjusted analyses.

Power and Sample Size

While 140 HCA hospitals are eligible for recruitment, we have HCA corporate commitment to assure the participation of at least 120 hospitals. Power was assessed using simulation methods. We simulated hospitals using information from HCA regarding ICU size and from a prior trial (REDUCE MRSA Trial) regarding likely rates of *S. aureus* in the baseline period. With 120 hospitals, we will have 82% power to detect non-inferiority within a hazard ratio of 1.1, based upon 2014 HCA ICU-attributable *S. aureus* clinical cultures of 4.8 cases per 1,000 ICU-days. While the intent is to confirm non-inferiority, we assume that iodophor will eradicate 5% more *S. aureus* than mupirocin due to existing mupirocin resistance. We estimate that total ICU patients in the intervention period will be ~171,500 patients who stay >2 ICU days.

NOTE: This statistical analytic plan was updated post-completion of the trial, but prior to accessing the trial dataset for cleaning or analysis. It was updated in response to the Harrington et al. (NEJM 2019;381:285-6) publication on “New Guidelines for Statistical Reporting in the *Journal.*”