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Utilizing nasal povidone-iodine to prevent bloodstream infections and transmission of Staphylococcus aureus among hemodialysis patients: a stepped-wedge cluster randomized control trial protocol.

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Title: Utilizing nasal povidone-iodine to prevent bloodstream infections and transmission of *Staphylococcus aureus* among hemodialysis patients: a stepped-wedge cluster randomized control trial protocol.

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Abstract

Introduction Over the past decade, rates of hospital-onset *Staphylococcus aureus* infections have decreased markedly. By contrast, rates of community-onset *S. aureus* infections have not improved at the same level, signifying the need for

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interventions beyond current hospital-based infection prevention strategies. Approximately 38% of hemodialysis patients carry *S. aureus* in their noses, and carriers have a nearly four-fold increased risk of *S. aureus* access-related bloodstream infections (BSI) compared with non-carriers. Our objective is to determine the clinical efficacy and effectiveness of a novel intervention using nasal povidone-iodine (PVI) to prevent BSIs among patients on hemodialysis. We will survey patients and conduct qualitative interviews with healthcare workers to identify barriers and facilitators to implementing the intervention.

Methods and Analysis We will perform an open-label, stepped-wedge cluster randomized trial (CRT) to assess the effectiveness of nasal PVI compared with standard care. Sixteen outpatient hemodialysis units will participate in the study. The three-year trial period will be divided into a four-month baseline period and eight additional four-month time blocks. The primary outcome of the study will be *S. aureus* BSI, defined as a *S. aureus* positive blood culture collected in the outpatient setting or within one calendar day after a hospital admission. The study team will evaluate characteristics of individual patients and the clusters by exposure status (control or intervention) to assess the balance between groups, and calculate descriptive statistics such as average responses separately for control and intervention survey questions.

Ethics and Dissemination This study has received IRB approval from all study sites. A Data Safety and Monitoring Board will monitor this multicenter clinical trial. We will present our results at international meetings. The study team will publish findings in peer-reviewed journals and make each accepted peer-reviewed manuscript publicly available.

Trial Registration Number NCT04210505

Article Summary

Strengths and Limitations of This Study

- Novel intervention targets a modifiable risk factor for *S. aureus* bloodstream infections nasal carriage in patients on hemodialysis.
- Stepped-wedge Cluster Randomized Trial design allows units to serve as their own controls and as a control for other units, thus limiting selection bias and imbalance among the intervention and control units.
- Nasal Povidone-Iodine (PVI) suppresses bacteria for only 12-24 hours and must be reapplied before each procedure.

INTRODUCTION

Over the past decade, rates of hospital-onset *Staphylococcus aureus* infections have decreased markedly.[1,2] By contrast, rates of community-onset *S. aureus* infections have not improved at the same level. The U.S. Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC NHSN) reported that 83% of methicillin-resistant *S. aureus* (MRSA) bloodstream infections were community-onset infections, signifying the need for interventions beyond current hospital-based infection prevention strategies.[3]

Patients on chronic hemodialysis are an ideal target population in whom to implement interventions to decrease rates of healthcare-associated, community-onset *S. aureus* infections. More than 400,000 patients received hemodialysis in 2018, and the majority of these patients received in-center hemodialysis.[4] Between 2005 and 2008, 43% of patients on hemodialysis tracked in the U.S. Renal Data System were hospitalized for infection-related diagnoses.[5] Approximately 30% of bloodstream infections (BSI) among patients on hemodialysis are caused by *S. aureus* [6,7] and these infections cause considerable morbidity [8-11] and mortality.[10,12]

Several factors increase the risk for *S. aureus* infections among patients on hemodialysis. First, a substantial proportion (38%) of these patients carry *S. aureus* in their noses, and carriers have a nearly four-fold increased risk of *S. aureus* access-related BSI compared with non-carriers.[13] Second, these patients have impaired immune function, which makes them more susceptible to infection.[14] Third, *S. aureus* can colonize the skin on

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patients' vascular access sites (arteriovenous grafts or fistulae) and this organism can be introduced into the bloodstream when the skin is punctured or dialysis catheters are accessed.[15-18] Fourth, the *S. aureus* colonizing one patient can be transmitted to other patients in the same hemodialysis unit. We previously found that 87% of patients on dialysis who carried *S. aureus* in their noses and on their hands carried the same strains at both sites, suggesting transmission from the patients' noses to their skin.[19] The *S. aureus* strains can then be transmitted from patient-to-patient in a hemodialysis unit via direct contact between patients and healthcare workers' (HCWs) hands and indirectly by contaminated furniture and equipment.[20] Unlike many other risk factors for BSI in this patient population (e.g., comorbidities), *S. aureus* nasal carriage is modifiable and thus our intervention could substantially benefit this population.[5,6,21]

To date, studies that evaluated nasal decolonization of patients on hemodialysis assessed the efficacy of intranasal mupirocin ointment for decolonization and infection prevention.[22] However, few dialysis centers have included mupirocin decolonization as a standard practice due to implementation barriers such as concern for mupirocin resistance and complicated protocols.[22-25] Povidone-Iodine (PVI) has been used as an antiseptic in the healthcare setting for decades and PVI resistance has not been found.[26,27] Thus, nasal PVI can be given to all patients who are not allergic to iodine regardless of their colonization status. 5% PVI (w/w [0.5% available iodine] USP) is available under the U.S. Food and Drug Administration Final Rule.[28] Our objective is to perform a multicenter stepped-wedge cluster randomized trial (CRT) to determine the clinical efficacy and effectiveness of a novel intervention using nasal PVI to prevent BSIs among patients on hemodialysis. We will survey patients and conduct qualitative interviews with HCWs to identify barriers and facilitators to implementing the intervention.

TRIAL OBJECTIVES

This trial is registered with ClinicalTrials.gov (NCT04210505).

Objective 1: Conduct a multicenter, stepped-wedge cluster randomized trial to determine whether nasal PVI decolonization reduces infections among patients on hemodialysis.

Objective 2: Survey patients to assess their satisfaction with nasal PVI decolonization, assess PVI's role in patient activation around their own health before and after PVI use, and identify barriers and facilitators to implementation.

Objective 3: Examine HCW satisfaction with implementation of nasal PVI decolonization and assess barriers and facilitators to the process via qualitative interviews and site visits.

METHODS AND ANALYSIS

Study Design

We will perform an open-label, stepped-wedge cluster randomized trial (CRT) to assess the effectiveness of nasal PVI compared with standard care. Our objectives are to evaluate whether using intranasal PVI will reduce rates of *S. aureus* BSI among patients on hemodialysis, to qualitatively evaluate the implementation of this intervention, and to measure HCW and patient satisfaction with PVI. We will randomly assign when hemodialysis units (clusters) will cross over from the control group to the intervention group such that all units will eventually receive the intervention.[29] The control group will consist of standard care as regulated by U.S. Centers for Medicare and Medicaid Services (CMS). We will include new patients who begin hemodialysis and stop patient follow-up when a patient is no longer on hemodialysis (e.g., recovery of kidney function, kidney transplantation, or death).[5]

Sixteen outpatient hemodialysis units will participate in the study. The three-year trial period will be divided into a four-month baseline period and eight additional four-month time blocks (TABLE 1). All units will begin in the control condition (C; no intervention). Two units (a unit pair) will be added to the intervention (I) in a stepwise fashion at the beginning of the eight additional time blocks.[29]

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TABLE 1. Stepped-Wedge Cluster Randomized Trial Study Design

	Baseline *Months 1-4*	Block 1 *Months 5-8*	Block 2 *Months 9-12*	Block 3 *Months 13-16*	Block 4 *Months 17-20*	Block 5 *Months 21-24*	Block 6 *Months 25-28*	Block 7 *Months 29-32*	Block Months 33-36
Unit Pair 1	C	I	I	I	I	I	I	I	I
Unit Pair 2	C	C	I	I	I	I	I	I	I
Unit Pair 3	C	C	C	I	I	I	I	I	I
Unit Pair 4	C	C	C	C	I	I	I	I	I
Unit Pair 5	C	C	C	C	C	I	I	I	I
Unit Pair 6	C	C	C	C	C	C	I	I	I
Unit Pair 7	C	C	C	C	C	C	C	I	I
Unit Pair 8	C	C	C	C	C	C	C	C	I

Study Setting and Participants

The proposed research will be performed at outpatient hemodialysis units affiliated with five U.S. academic medical centers in the Southeast, Midwest, and Northeast. This multicenter study of geographically diverse hospital systems and their patient populations will improve the external validity of our study.

We will enroll patients if they are 18 years or older and receiving outpatient chronic hemodialysis (3 sessions a week). We will exclude patients receiving peritoneal dialysis or home hemodialysis, patients with documented or verbalized sensitivity or allergy to iodine or iodine-based contrast, patients with known pregnancy, and patients on treatment for bacterial infection. We will enroll adult HCWs working at any of the 16 hemodialysis units who are willing to participate in the semi-structured interviews.

Screening and Recruitment

Research team members at each dialysis center will identify patients that meet inclusion criteria and will discuss the study with patients during a hemodialysis session, while ensuring that patient care is not delayed or disrupted. This study was approved with a waiver of signed consent. Thus, patients who verbally agree to the informed consent will be included in the study.

Two research team anthropologists will schedule and conduct semi-structured interviews with 5-10 HCW at hemodialysis units across the five sites to examine the contextual factors that influence adoption of nasal PVI decolonization. The anthropologists will ask each unit's medical director for permission to interview staff and for the names of potential interviewees. The anthropologists will invite potential interviewees—the nurse manager, a physician, nurses, nursing assistants, or technicians—to participate.

This study has received institutional IRB approval from the University of Iowa and site-specific IRB approval, including waiver of documentation of informed consent. We will offer participants the opportunity to talk with the treating physician or their family member before consenting. Study participation will not influence the standard of care subjects would otherwise receive for their disease process. To minimize risks, all subjects will be carefully pre-screened to identify any factors that could contribute to increased risk. We will store all confidential information in locked offices and store electronic data on password protected computers only available to study team members. Participants will receive study team members' contact information.

Sample Size and Power

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We used the method described by Hussey and Hughes to calculate the sample size and the study's power.[30] As described above, the stepped-wedge study will last 36 months (time points) with data collected monthly from 16 sites (clusters). After the baseline period, two sites will transition to the intervention at the start of each subsequent four-month block. Our pilot data suggested that approximately 1,825 patients will receive hemodialysis at any given time across all sites, with approximately 100 patients per site per time point (N). We estimated the between site variability as $\tau^2 = 0.01$. Given that 3% of patients who received hemodialysis at our study sites during 2016 acquired *S. aureus* BSI, we estimated the within-site variability to be 0.00029. Thus, we estimated that we will have 98% power to see a change in the rate of *S. aureus* BSI from 3% to 2% (absolute difference=1%, odds ratio [OR]=0.66). This difference is more conservative than the difference seen in prior mupirocin decolonization studies among patients on hemodialysis (OR=0.32 to 0.51).[22] Our pilot data indicated that 30% of patients on hemodialysis at our study sites were dialyzed through central venous catheters, 5% of whom acquired *S. aureus* BSI in 2016. Given this information, we estimated that a subset analysis of patients dialyzed through catheters will have 99% power to identify a decrease in infections from 5% to 2% (absolute difference=3%, OR=0.40).

Randomization

We paired dialysis units into 2-unit blocks according to two rules: 1) The dialysis units in a pair were not within the same geographic region; and 2) The approximate total monthly unique patients in a given unit block would be approximately 150 patients. Two study team members independently created the dialysis unit blocks and they minimized the variation from the ideal unit block size when their pairings disagreed. After we created the 2-unit block pairs, we used the sample function in R without replacement to randomize the order in which the pairs would enter the intervention phase. Each unit block had the same probability of selection. We stored the final randomization in a password protected file. Only the two team members who performed the randomization and 3M, which must coordinate delivery of the product to the participating sites in accordance with the project timeline, have access to that file. We will notify sites four months before their planned intervention start date.

Intervention

Events and procedures for hemodialysis subjects will occur over 4 research visits (TABLE 2). Research personnel will visit the dialysis centers four times over the study period.

Visit 1: Approximately a month before a dialysis center is scheduled to begin the intervention, a study team member will visit the dialysis center. During the visit, the study team member will describe the study, obtain verbal informed consent from patients present, and administer the pre-intervention (control) survey to all patients on hemodialysis who agree to participate. A study team member also will swab participants' noses to identify patients who carry *S. aureus* at baseline.

Visit 2: When a dialysis center is scheduled to begin the intervention, study personnel will obtain verbal informed consent from patients present and give each participating patient their first bottles of PVI, 4 applicators, and illustrated instructions for use. Patients will be encouraged to apply the PVI to their own noses, but they can also ask a nurse or technician for assistance.

Visit 3: After a dialysis session has begun and after obtaining verbal informed consent from the patient, a study team member will administer the first intervention survey to the patient. This intervention survey will assess acceptability of PVI approximately one month after the intervention has started.

Visit 4: Approximately 5 months after the beginning of the intervention and after obtaining verbal informed consent from the patient, a study team member will administer the second intervention survey. The two intervention surveys will ask the same questions and will be performed in the same manner. The results of the control period survey and the two intervention period surveys for each patient can be linked together.

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***S. aureus* point prevalence studies:** Each hemodialysis unit will collect nasal swabs from each participating hemodialysis patient's nose during the baseline period and twice per year over the 3-year study period (total of 6 times including baseline) we will collect nasal swabs to determine *S. aureus* colonization status.

Healthcare worker interview: Two members of the research team will conduct semi-structured in-person interviews with staff during site visits. The semi-structured interviews will include open-ended questions to explore domains including barriers and facilitators to implementing the intervention, provider and patient compliance with PVI decolonization, and the acceptability and feasibility of PVI decolonization. Interviews will be audio-recorded with the healthcare workers' permission and transcribed.

TABLE 2. Schedule of Events Table for both hemodialysis and healthcare worker visits.

Event	Visit 1	Visit 2	Visit 3	Visit 4	Each dialysis appointment	Every 6 months[a]	Once
Review of inclusion/exclusion criteria and lab results to confirm subject eligibility	X	X					
Testing for *Staphylococcus aureus* nasal carriage	X					X	
Pre-intervention Survey	X						
Povidone-iodine administration		X			X		
Intervention Survey			X	X			
Healthcare worker interview							X

a. **A study member will obtain the nasal swabs during the subject's dialysis sessions. This is in addition to the povidone-iodine administration.**

Outcomes and Data Collection

Primary Outcome: The primary outcome of the study will be *S. aureus* BSI, defined as a *S. aureus* positive blood culture collected in the outpatient setting or within one calendar day after a hospital admission. This outcome is collected every month by dialysis staff or infection prevention staff at each hospital system in accordance with CDC NHSN and the U.S. Centers for Medicare and Medicaid Services (CMS) requirements. These data will be shared with the study team and validated via chart review.

Secondary Outcomes: Definitions of secondary outcomes are presented in TABLE 3. They include:

- All BSIs among study patients, all access-related BSIs among study patients, all local access site infections among study patients.
- *S. aureus* nasal colonization[31]
- Patient satisfaction with nasal PVI
- Healthcare worker satisfaction with the intervention and barriers and facilitators to implementation of the intervention that the healthcare workers identified

TABLE 3: Definitions of Primary and Secondary Outcomes (CDC NHSN Definitions)

Bloodstream infection	A positive blood specimen collected in the outpatient setting or within 1 calendar day after a hospital admission
Access related bloodstream infection (ARBSI)	A bloodstream infection with the suspected source reported as the vascular access or uncertain

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***S. aureus* ARBSI**	An ARBSI in which the blood specimen was determined to be *S. aureus*
Local access site infection	Pus, redness or increased swelling at the vascular access site when an ARBSI is not present
***S. aureus* colonization**	The presence of *S. aureus* in the nares.

During each site's intervention period, a member of the study team will swab each participant's nares during their hemodialysis session after the patient applies PVI to determine if patients are colonized with *S. aureus* after applying PVI and during the at-risk period. *S. aureus* isolates will be tested for methicillin-susceptibility and the research team will perform pulsed field gel electrophoresis (PFGE) on all nasal isolates and if available, bloodstream isolates to assess whether serial isolates from the same patient are related, whether isolates from different patients in the same dialysis unit are related, and whether nasal isolates and infecting isolates from the same patient are identical. A sample of *S. aureus* isolates will be evaluated using whole genome sequencing.

Statistical and Ethnographic Analysis

Objective 1: The study team will evaluate characteristics of individual patients and the clusters by exposure status (control or intervention) to assess the balance between groups. As most participants will take part in both settings, paired t-tests, McNemar's test and repeated measures ANOVA will be used as appropriate. The overall proportion of unique patients in the control group who acquire infections compared with the intervention group will be assessed via McNemar's Test.

In the primary analysis, the study team will use a generalized linear mixed model (GLMM) with a logit link function to perform an analysis at the individual patient level evaluating the association between nasal povidone-iodine and *S. aureus* BSI. The model will include step and intervention indicators as fixed effects and a random intercept for cluster to account for hospital dependence. The study team will statistically adjust for important confounding variables, such as dialysis access type. The study team will perform an intention-to-treat analysis, assuming all patients received nasal PVI during the intervention periods. Patients who stop using PVI will be included in the study and evaluated for outcomes in this intention-to-treat analysis. Reasons for study "drop-out" such as death or renal transplant are not related to the intervention. However, the study team will model time to drop-out to characterize this patient population. An analysis will also be performed among patients who met the inclusion criteria, agreed to participate in the study, and received at least one dose of PVI.

Because patients who receive hemodialysis through central venous catheters are at the highest risk of infection, the study team use the GLMM methods described above to evaluate the association between nasal PVI and *S. aureus* BSI stratified by dialysis access type. The study team will also perform exploratory analyses to assess the effect of rural versus urban hemodialysis units and the effect of nasal PVI on methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) BSIs separately. Finally, the study team will evaluate the effect of nasal PVI on the secondary outcomes: all BSI caused by any pathogen, all BSI caused by any pathogen, local access site infection and vascular access infection. The study team will use SAS 9.4 (Cary, NC) for all analyses.

Objective 2: The study team will calculate descriptive statistics for control and intervention survey questions. They will use a two-sample Fisher's exact test to assess differences in the patients' responses to specific questions during the control and intervention periods. The study team will use bivariable and multivariate regression analysis to explore associations between survey measures and covariates.

Objective 3: Investigators will read a subset of transcripts and generate a preliminary codebook using an integrated approach to thematic analysis that includes a priori project-specific thematic codes, Consolidated Framework for Implementation Research (CFIR) constructs, and inductive codes identified during team discussions. Thereafter, the team will code documents, then iteratively adapt the codebook, conduct preliminary

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analyses, adapt the interview guide if needed, and gauge whether data saturation (i.e., no new themes or patterns emerge) has been reached. If data saturation has not been attained or if new areas are identified, we will perform, record, and analyze additional telephone interviews. The team will document codebook changes and the rationale for each change and will keep an audit trail.

Patient and Public Involvement

Neither patients nor members of the public participated in designing this study.

Ethics and Dissemination

The risk to patients is low in this study; however, a Data and Safety Monitoring Board (DSMB) will oversee this study. The DSMB will be made up of clinical, biostatistical, infectious disease, and renal disease experts who are approved by the Agency for Health Research and Quality (AHRQ). Occurrence of adverse events will be monitored throughout the trial and will cover all randomized subjects. To protect confidentiality, we will assign each subject a study ID. All electronic files are stored on password protected computers that are connected to a secured shared drive. Nasal swabs will be labeled with a coding descriptor, and no PHI will be collected from the lab. The isolates will be discarded after the results are finalized. Only the PI, data analysts, statistician, and the DSMB will have access to the final trial data set. Site Principal Investigators will have direct access to their own site's data sets, and will have access to other sites' data by request. In Year 5 of the study, we will present our results at international meetings. We will publish our findings in peer-reviewed journals and make each peer-reviewed accepted manuscript publicly available.

DISCUSSION

Prior studies have found that nasal decolonization with mupirocin reduced infection rates among patients on hemodialysis.[16,19,22] For example, Weiner et al. (2016) demonstrated that nasal mupirocin was associated with a 4-fold reduction in *S. aureus* bloodstream infections in this patient population.[32] However, consistent use of mupirocin can lead to mupirocin-resistant *S. aureus*.[16] A meta-analysis found that decolonization with mupirocin was associated with a 59% reduction in *S. aureus* infections among dialysis patients, but up to 10% of patients who used mupirocin become colonized with a mupirocin-resistant *S. aureus* strain.[22] Given that mupirocin prophylaxis can increase the frequency of mupirocin-resistant *S. aureus* isolates, and that the mupirocin decolonization protocol is often difficult to implement, most hemodialysis units do not routinely decolonize patients with mupirocin.[22]

Nasal PVI may be preferred over mupirocin for long-term prevention of *S. aureus* infections because it is easy to use and it has multiple targets of action—thus, the risk of PVI resistance among *S. aureus* isolates is minimal.[26,33-35] PVI has been used in healthcare for years for skin antisepsis. Recently, small, single center studies found that nasal PVI was associated with decreased surgical site infection rates, and that surgical patients preferred this product over mupirocin because it had fewer side effects and was more pleasant.[36-39] Some investigators have used PVI at hemodialysis catheter exit sites or for catheter care.[40,41] However, no published studies have evaluated nasal PVI for decolonizing patients on hemodialysis.

Our objectives are to evaluate whether decolonizing patients' noses with PVI will reduce rates of *S. aureus* BSI among patients on hemodialysis, to qualitatively evaluate the implementation of this intervention, and to assess patient and healthcare worker satisfaction with PVI. This trial will be performed at 16 outpatient hemodialysis units affiliated with five academic medical centers. These ambulatory hemodialysis units are geographically dispersed and care for both rural and urban patients who receive chronic care.

We chose the stepped-wedge CRT design for multiple reasons. First, since nasal PVI could prevent endogenous *S. aureus* infection and could prevent exogenous transmission of this organism from patient to patient, individual randomization would not allow us to adequately assess the full effect of this intervention. Second, units will serve as their own controls and as controls for other units, thus limiting selection bias and imbalance among the intervention and control units.[29] Third, the staggered starting dates can help us measure and adjust for temporal biases such as the effect of CMS policy changes that occur during the study period.

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Limitations

The proposed study has three main limitations. First, nasal PVI suppresses bacteria for only 12-24 hours.[35] Thus, PVI must be reapplied before each procedure. Second, we will not compare PVI with mupirocin. Instead, our control group will be standard care, which is justified because mupirocin has not been routinely used for preventing BSI among patients on hemodialysis due to implementation barriers. Third, PVI is considered a novel intervention for patients on hemodialysis, and thus we are required to obtain informed consent from each patient. Therefore, patients who do not consent to using nasal PVI could transmit *S. aureus* to patients who do participate in the intervention.

Significance

Nasal PVI is currently used in many hospitals to prevent surgical site infections. Our study evaluates this product in a new patient population. This large stepped-wedge cluster randomized trial aims to determine whether nasal PVI decreases rates of *S. aureus* BSI among patients on hemodialysis, and to collect data on barriers and facilitators to implementation. Given that PVI as widely available and inexpensive, is easy to use and implement, and does not cause resistance, this intervention could be more generalizable than mupirocin ointment. An effective intervention to prevent infections among patients on hemodialysis could improve outcomes among the 2 million people who receive renal replacement therapy worldwide.[42]

Trial Status

Trial is currently ongoing.

Funding Statement

This work was supported by the Agency for Health Research and Quality (AHRQ) grant number 1R01HS026724-01 and by the National Center For Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR002537. Povidone-iodine product will be donated by 3M funding number ISR74. AHRQ, NIH and 3M have no role in study design; collection, management, analysis, and interpretation of data; writing of the report; nor the decision to submit the report for publication.

Competing Interests: None declared.

Author Contributions: Study design: MS, RN, KD, LH, AO, LB, DD, JC, JJ, DP, SB, AV, AM, MF, DOM. Study implementation: MS, MW, RN, KD, AR, LB, JC, JJ, DP, SB, AV, AM, MF, PT, MM, EJ. Statistical analysis: RN, AO. All authors contributed to, read and approved the final manuscript. Dr. Schweizer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A; complete (please see ClinicalTrials.gov page)
Protocol version	#3	Date and version identifier	N/A; no version identifier
Funding	#4	Sources and types of financial, material, and other support	9

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Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2, 3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3, 9
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3

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Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4 (ClinicalTrials.gov)
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	3, 7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6 (study includes qualitative component to assess intervention implementation)
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A; intervention does not affect care usually received
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7

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Participant timeline	#13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrollment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A (not blinded)

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Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A (study is not blinded)
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6, 7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6, 7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised	7

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		analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	N/A (Study is IRB approved)
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 5

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Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A (no ancillary studies included)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A (no provisions provided; please see attached consent form)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A (no intended use of professional writers)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form attached
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or	5, 6, 7, 8

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molecular analysis in the current trial and for future use in ancillary studies, if applicable

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Utilizing nasal povidone-iodine to prevent bloodstream infections and transmission of Staphylococcus aureus among hemodialysis patients: a stepped-wedge cluster randomized control trial protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-048830.R1
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Title: Utilizing nasal povidone-iodine to prevent bloodstream infections and transmission of *Staphylococcus aureus* among hemodialysis patients: a stepped-wedge cluster randomized control trial protocol.

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Keywords: povidone-iodine; *Staphylococcus aureus*; controlled clinical trials, randomized; hemodialysis; qualitative evaluation

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Abstract

Introduction Approximately 38% of hemodialysis patients carry *S. aureus* in their noses, and carriers have a nearly four-fold increased risk of *S. aureus* access-related bloodstream infections (BSI) compared with non-carriers. Our objective is to

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determine the clinical efficacy and effectiveness of a novel intervention using nasal povidone-iodine (PVI) to prevent BSIs among patients in hemodialysis units. We will survey patients and conduct qualitative interviews with healthcare workers to identify barriers and facilitators to implementing the intervention.

Methods and Analysis We will perform an open-label, stepped-wedge cluster randomized trial (CRT) to assess the effectiveness of nasal PVI compared with standard care. Sixteen outpatient hemodialysis units will participate in the study. The three-year trial period will be divided into a four-month baseline period and eight additional four-month time blocks. The primary outcome of the study will be *S. aureus* BSI, defined as a *S. aureus* positive blood culture collected in the outpatient setting or within one calendar day after a hospital admission. The study team will evaluate characteristics of individual patients and the clusters by exposure status (control or intervention) to assess the balance between groups, and calculate descriptive statistics such as average responses separately for control and intervention survey questions.

Ethics and Dissemination This study has received IRB approval from all study sites. A Data Safety and Monitoring Board will monitor this multicenter clinical trial. We will present our results at international meetings. The study team will publish findings in peer-reviewed journals and make each accepted peer-reviewed manuscript publicly available.

Trial Registration Number NCT04210505

Article Summary

Strengths and Limitations of This Study

- Novel intervention targets a modifiable risk factor for *S. aureus* bloodstream infections in patients on hemodialysis.
- Stepped-wedge Cluster Randomized Trial design allows units to serve as their own controls and as a control for other units, thus limiting selection bias and imbalance among the intervention and control units.
- Nasal Povidone-Iodine (PVI) suppresses bacteria for only 12-24 hours and must be reapplied before each procedure.

INTRODUCTION

————Patients on chronic hemodialysis are an ideal target population in whom to implement interventions to decrease rates of *S. aureus* infections. More than 400,000 patients received hemodialysis in 2018, and the majority of these patients received in-center hemodialysis.[1] Between 2005 and 2008, 43% of patients on hemodialysis tracked in the U.S. Renal Data System were hospitalized for infection-related diagnoses.[2] Approximately 30% of bloodstream infections (BSI) among patients on hemodialysis are caused by *S. aureus* [3,4] and these infections cause considerable morbidity [5-8] and mortality.[7,9]

Several factors increase the risk for *S. aureus* infections among patients on hemodialysis. First, a substantial proportion (38%) of these patients carry *S. aureus* in their noses, and carriers have a nearly four-fold increased risk of *S. aureus* access-related BSI compared with non-carriers.[10] Second, these patients have impaired immune function, which makes them more susceptible to infection.[11] Third, *S. aureus* can colonize the skin on patients' vascular access sites (arteriovenous grafts or fistulae) and this organism can be introduced into bloodstream when the skin is punctured or dialysis catheters are accessed.[12-15] Fourth, the *S. aureus* colonizing one patient can be transmitted to other patients in the same hemodialysis unit. We previously found that 87% of patients on dialysis who carried *S. aureus* in their noses and on their hands carried the same strains at both sites, suggesting transmission from the patients' noses to their skin.[16] The *S. aureus* strains can then be transmitted from patient-to-patient in a hemodialysis unit via direct contact between patients and healthcare workers' (HCWs) hands and indirectly by contaminated furniture and equipment.[17] Unlike many other risk factors for BSI in this patient population (e.g., comorbidities), *S. aureus* nasal carriage is modifiable and thus our intervention could substantially benefit this population.[2,3,18]

To date, studies that evaluated nasal decolonization of patients on hemodialysis assessed the efficacy of intranasal

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mupirocin ointment for decolonization and infection prevention.[19] However, few dialysis centers have included mupirocin decolonization as a standard practice due to implementation barriers such as concern for mupirocin resistance and complicated protocols.[19-22] Povidone-Iodine (PVI) has been used as an antiseptic in the healthcare setting for decades and PVI resistance has not been found.[23,24] Thus, nasal PVI can be given to all patients who are not allergic to iodine regardless of their colonization status. 5% PVI (w/w [0.5% available iodine] USP) is available under the U.S. Food and Drug Administration Final Rule.[25] Our objective is to perform a multicenter stepped-wedge cluster randomized trial (CRT) to determine the clinical efficacy and effectiveness of a novel intervention using nasal PVI to prevent BSIs among patients on hemodialysis. We will survey patients and conduct qualitative interviews with HCWs to identify barriers and facilitators to implementing the intervention.

TRIAL OBJECTIVES

This trial is registered with ClinicalTrials.gov (NCT04210505).

Objective 1: Conduct a multicenter, stepped-wedge cluster randomized trial to determine whether nasal PVI decolonization reduces infections among patients on hemodialysis.

Objective 2: Survey patients to assess their satisfaction with nasal PVI decolonization, assess PVI's role in patient activation around their own health before and after PVI use, and identify barriers and facilitators to implementation.

Objective 3: Examine HCW satisfaction with implementation of nasal PVI decolonization and assess barriers and facilitators to the process via qualitative interviews and site visits.

METHODS AND ANALYSIS

Study Design

We will perform an open-label, stepped-wedge cluster randomized trial (CRT) to assess the effectiveness of nasal PVI compared with standard care. Our objectives are to evaluate whether using intranasal PVI will reduce rates of *S. aureus* BSI among patients on hemodialysis, to qualitatively evaluate the implementation of this intervention, and to measure HCW and patient satisfaction with PVI. We will randomly assign when hemodialysis units (clusters) will cross over from the control group to the intervention group such that all units will eventually receive the intervention.[26] The control group will consist of standard care as regulated by U.S. Centers for Medicare and Medicaid Services (CMS). We will include new patients who begin hemodialysis and stop patient follow-up when a patient is no longer on hemodialysis (e.g., recovery of kidney function, kidney transplantation, or death).[2]

Sixteen outpatient hemodialysis units will participate in the study. The three-year trial period will be divided into a four-month baseline period and eight additional four-month time blocks (TABLE 1). All units will begin in the control condition (C; no intervention). Two units (a unit pair) will be added to the intervention (I) in a stepwise fashion at the beginning of the eight additional time blocks.[26]

TABLE 1. Stepped-Wedge Cluster Randomized Trial Study Design

	Baseline *Months 1-4*	Block 1 *Months 5-8*	Block 2 *Months 9-12*	Block 3 *Months 13-16*	Block 4 *Months 17-20*	Block 5 *Months 21-24*	Block 6 *Months 25-28*	Block 7 *Months 29-32*	Block 8 Months 33-36
Unit Pair 1	**C**	**I**	**I**	**I**	**I**	**I**	**I**	**I**	**I**
Unit Pair 2	**C**	**C**	**I**	**I**	**I**	**I**	**I**	**I**	**I**
Unit Pair 3	**C**	**C**	**C**	**I**	**I**	**I**	**I**	**I**	**I**

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Unit Pair 4	C	C	C	C	I	I	I	I	I
Unit Pair 5	C	C	C	C	C	I	I	I	I
Unit Pair 6	C	C	C	C	C	C	I	I	I
Unit Pair 7	C	C	C	C	C	C	C	I	I
Unit Pair 8	C	C	C	C	C	C	C	C	I

Study Setting and Participants

The proposed research will be performed at outpatient hemodialysis units affiliated with five U.S. academic medical centers in the Southeast, Midwest, and Northeast. This multicenter study of geographically diverse hospital systems and their patient populations will improve the external validity of our study. We have confirmed that none of the study sites currently perform nasal decolonization.

We will enroll patients if they are 18 years or older and receiving outpatient chronic hemodialysis (3 sessions a week). We will exclude patients receiving peritoneal dialysis or home hemodialysis, patients with documented or verbalized sensitivity or allergy to iodine or iodine-based contrast, patients with known pregnancy, and patients on treatment for bacterial infection. We will enroll adult HCWs working at any of the 16 hemodialysis units who are willing to participate in the semi-structured interviews.

Screening and Recruitment

Research team members at each dialysis center will identify patients that meet inclusion criteria and will discuss the study with patients during a hemodialysis session, while ensuring that patient care is not delayed or disrupted. This study was approved with a waiver of signed consent, as the study is deemed low-risk and patients may have trouble writing while receiving hemodialysis. Thus, patients who verbally agree to the informed consent will be included in the study.

Two research team anthropologists will schedule and conduct semi-structured interviews with 5-10 HCW at hemodialysis units across the five sites to examine the contextual factors that influence adoption of nasal PVI decolonization. The anthropologists will ask each unit's medical director for permission to interview staff and for the names of potential interviewees. The anthropologists will invite potential interviewees—the nurse manager, a physician, nurses, nursing assistants, or technicians—to participate.

This study has received institutional IRB approval from the University of Iowa and site-specific IRB approval, including waiver of documentation of informed consent. We will offer participants the opportunity to talk with the treating physician or their family member before consenting. Study participation will not influence the standard of care subjects would otherwise receive for their disease process. To minimize risks, all subjects will be carefully pre-screened to identify any factors that could contribute to increased risk. We will capture adherence to the intervention during repeated site visits and patient surveys administered throughout the intervention period, and we will record patient drop-out. We will store all confidential information in locked offices and store electronic data on password protected computers only available to study team members. Participants will receive study team members' contact information.

Sample Size and Power

We used the method described by Hussey and Hughes to calculate the sample size and the study's power.[27] As described above, the stepped-wedge study will last 36 months (time points) with data collected monthly from 16 sites (clusters). After the baseline period, two sites will transition to the intervention at the start of each subsequent four-month block. Our pilot data suggested that approximately 1,825 patients will receive hemodialysis at any given time across all sites, with approximately 100 patients per site per time point (N). We estimated the between site variability as $\tau^2 = 0.01$. Given that 3% of patients who received hemodialysis at our study sites during 2016 acquired *S. aureus* BSI, we estimated the within-site variability to be 0.00029. Thus, we estimated that we will have 98% power to see a change in the rate of *S. aureus* BSI from 3% to 2% (absolute difference=1%, odds ratio [OR]=0.66). This difference is more conservative than the difference

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seen in prior mupirocin decolonization studies among patients on hemodialysis (OR=0.32 to 0.51).[19] Our pilot data indicated that 30% of patients on hemodialysis at our study sites were dialyzed through central venous catheters, 5% of whom acquired *S. aureus* BSI in 2016. Given this information, we estimated that a subset analysis of patients dialyzed through catheters will have 99% power to identify a decrease in infections from 5% to 2% (absolute difference=3%, OR=0.40).

Randomization

We paired dialysis units into 2-unit blocks according to two rules: 1) The dialysis units in a pair were not within the same geographic region; and 2) The approximate total monthly unique patients in a given unit block would be approximately 150 patients. Two study team members independently created the dialysis unit blocks and they minimized the variation from the ideal unit block size when their pairings disagreed. After we created the 2-unit block pairs, we used the sample function in R without replacement to randomize the order in which the pairs would enter the intervention phase. Each unit block had the same probability of selection. We stored the final randomization in a password protected file. Only the two team members who performed the randomization and 3M, which must coordinate delivery of the product to the participating sites in accordance with the project timeline, have access to that file. We will notify sites four months before their planned intervention start date. The research team is well-connected with all sites and will prevent premature implementation of the intervention.

Intervention

Events and procedures for hemodialysis subjects will occur over 4 research visits (TABLE 2). Research personnel will visit the dialysis centers four times over the study period.

Visit 1: Approximately a month before a dialysis center is scheduled to begin the intervention, a study team member will visit the dialysis center. During the visit, the study team member will describe the study, obtain verbal informed consent from patients present, and administer the pre-intervention (control) survey to all patients on hemodialysis who agree to participate. A study team member also will swab participants' noses to identify patients who carry *S. aureus* at baseline.

Visit 2: When a dialysis center is scheduled to begin the intervention, study personnel will obtain verbal informed consent from patients present and give each participating patient their first disposable, single-use bottles of PVI, 4 applicators, and illustrated instructions for use. Participating patients will apply PVI at each hemodialysis appointment. Patients will be encouraged to apply the PVI to their own noses, but they can also ask a nurse or technician for assistance. Patients will also have the option to apply PVI at home.

Visit 3: After a dialysis session has begun and after obtaining verbal informed consent from the patient, a study team member will administer the first intervention survey to the patient. This intervention survey will assess acceptability of PVI approximately one month after the intervention has started.

Visit 4: Approximately 5 months after the beginning of the intervention and after obtaining verbal informed consent from the patient, a study team member will administer the second intervention survey. The two intervention surveys will ask the same questions and will be performed in the same manner. The results of the control period survey and the two intervention period surveys for each patient can be linked together.

***S. aureus* point prevalence studies:** Each hemodialysis unit will collect nasal swabs from each participating hemodialysis patient's nose during the baseline period and twice per year over the 3-year study period (total of 6 times including baseline) we will collect nasal swabs to determine *S. aureus* colonization status.

Healthcare worker interview: Two members of the research team will conduct semi-structured in-person interviews with staff during site visits. The semi-structured interviews will include open-ended questions to explore domains including barriers and facilitators to implementing the intervention, provider and patient compliance with PVI decolonization, and the acceptability and feasibility of PVI decolonization. Interviews will be audio-recorded with the healthcare workers'

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TABLE 2. Schedule of Events Table for both hemodialysis and healthcare worker visits.

Event	Visit 1	Visit 2	Visit 3	Visit 4	Each dialysis appointment	Every 6 months[a]	Once
Review of inclusion/exclusion criteria and lab results to confirm subject eligibility	X	X					
Testing for *Staphylococcus aureus* nasal carriage	X					X	
Pre-intervention Survey	X						
Povidone-iodine administration		X			X		
Intervention Survey			X	X			
Healthcare worker interview							X

a. **A study member will obtain the nasal swabs during the subject's dialysis sessions. This is in addition to the povidone-iodine administration.**

Outcomes and Data Collection

Primary Outcome: The primary outcome of the study will be *S. aureus* BSI, defined as a *S. aureus* positive blood culture collected in the outpatient setting or within one calendar day after a hospital admission. This outcome is collected every month by dialysis staff or infection prevention staff at each hospital system in accordance with The U.S. Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC NHSN) and the U.S. Centers for Medicare and Medicaid Services (CMS) requirements. These data will be shared with the study team and validated via chart review.

Secondary and Additional Outcomes: Definitions of secondary outcomes are presented in TABLE 3 with additional evaluated outcomes presented in TABLE 4.

TABLE 3: Definitions of Secondary Outcomes (CDC NHSN Definitions)

Bloodstream infection (BSI)	A positive blood specimen collected in the outpatient setting or within 1 calendar day after a hospital admission
Access related bloodstream infection (ARBSI)	A bloodstream infection with the suspected source reported as the vascular access or uncertain
***S. aureus* ARBSI**	An ARBSI in which the blood specimen was determined to be *S. aureus*
Local access site infection	Pus, redness or increased swelling at the vascular access site when an ARBSI is not present
***S. aureus* local access site infection**	Pus, redness or increased swelling at the vascular access site when an ARBSI is not present but with positive culture for *S. aureus.*
***S. aureus* BSI among intervention participants**	An *S. aureus* positive blood specimen collected in the outpatient setting or within 1 calendar day after a hospital admission from patients participating in the intervention.

TABLE 4: Additional Outcomes Evaluated

Patient Satisfaction with nasal PVI	Barriers and facilitators to the intervention collected from patients through qualitative surveys.
Healthcare worker satisfaction with intervention	Barriers and facilitators to the intervention collected through qualitative interviews with healthcare workers.

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***S. aureus* colonization**	The presence of *S. aureus* in the nares.

During each site's intervention period, a member of the study team will swab each participant's nares during their hemodialysis session after the patient applies PVI to determine if patients are colonized with *S. aureus* after applying PVI and during the at-risk period. *S. aureus* isolates will be tested for methicillin-susceptibility and the research team will perform pulsed field gel electrophoresis (PFGE) on all nasal isolates and if available, bloodstream isolates to assess whether serial isolates from the same patient are related, whether isolates from different patients in the same dialysis unit are related, and whether nasal isolates and infecting isolates from the same patient are identical. A sample of *S. aureus* isolates will be evaluated using whole genome sequencing. Laboratory testing will occur in a single laboratory using standardized methodology.

Statistical and Ethnographic Analysis

Objective 1: The study team will evaluate characteristics of individual patients and the clusters by exposure status (control or intervention) to assess the balance between groups. As most participants will take part in both settings, paired t-tests, McNemar's test and repeated measures ANOVA will be used as appropriate. The overall proportion of unique patients in the control group who acquire infections compared with the intervention group will be assessed via McNemar's Test.

In the primary analysis, the study team will use a generalized linear mixed model (GLMM) with a logit link function to perform an analysis at the individual patient level evaluating the association between nasal povidone-iodine and *S. aureus* BSI. The model will include step and intervention indicators as fixed effects and a random intercept for cluster to account for hospital dependence. The study team will statistically adjust for important confounding variables, such as dialysis access type. The study team will perform an intention-to-treat analysis, assuming all patients received nasal PVI during the intervention periods. Patients who stop using PVI will be included in the study and evaluated for outcomes in this intention-to-treat analysis. Reasons for study "drop-out" such as death or renal transplant are not related to the intervention. However, the study team will model time to drop-out to characterize this patient population. An analysis will also be performed among patients who met the inclusion criteria, agreed to participate in the study, and received at least one dose of PVI.

Because patients who receive hemodialysis through central venous catheters are at the highest risk of infection, the study team use the GLMM methods described above to evaluate the association between nasal PVI and *S. aureus* BSI stratified by dialysis access type. The study team will also perform exploratory analyses to assess the effect of rural versus urban hemodialysis units and the effect of nasal PVI on methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) BSIs separately. Finally, the study team will evaluate the effect of nasal PVI on the secondary outcomes: all BSI caused by any pathogen, all BSI caused by any pathogen, local access site infection and vascular access infection. The study team will use SAS 9.4 (Cary, NC) for all analyses.

Objective 2: The study team will calculate descriptive statistics for control and intervention survey questions. They will use a two-sample Fisher's exact test to assess differences in the patients' responses to specific questions during the control and intervention periods. The study team will use bivariable and multivariate regression analysis to explore associations between survey measures and covariates.

Objective 3: Investigators will read a subset of transcripts and generate a preliminary codebook using an integrated approach to thematic analysis that includes a priori project-specific thematic codes, Consolidated Framework for Implementation Research (CFIR) constructs, and inductive codes identified during team discussions. Thereafter, the team will code documents, then iteratively adapt the codebook, conduct preliminary analyses, adapt the interview guide if needed, and gauge whether data saturation (i.e., no new themes or patterns emerge) has been reached. If data saturation has not been attained or if new areas are identified, we will perform, record, and analyze additional telephone interviews. The team will document codebook changes and the rationale for each change and will keep an audit trail.

Patient and Public Involvement

Neither patients nor members of the public participated in designing this study.

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Ethics and Dissemination

The risk to patients is low in this study; however, a Data and Safety Monitoring Board (DSMB) will oversee this study. The DSMB will be made up of clinical, biostatistical, infectious disease, and renal disease experts who are approved by the Agency for Health Research and Quality (AHRQ). Occurrence of adverse events will be monitored throughout the trial by surveys and the study team, and will cover all randomized subjects. Rare allergy to PVI will be treated by hemodialysis staff if needed. This is a Phase IV study of an antiseptic that is available under the Food and Drug Administration (FDA) Final Rule (Federal Register December 20, 2017)[25] Any potential side effects from PVI will be captured through patient surveys. To protect confidentiality, we will assign each subject a study ID. All electronic files are stored on password protected computers that are connected to a secured shared drive. Nasal swabs will be labeled with a coding descriptor, and no PHI will be collected from the lab. The isolates will be discarded after the results are finalized. Only the PI, data analysts, statistician, and the DSMB will have access to the final trial data set. Site Principal Investigators will have direct access to their own site's data sets, and will have access to other sites' data by request. In Year 5 of the study, we will present our results at international meetings. We will publish our findings in peer-reviewed journals and make each peer-reviewed accepted manuscript publicly available.

DISCUSSION

Prior studies have found that nasal decolonization with mupirocin reduced infection rates among patients on hemodialysis.[13,16,19] For example, Weiner et al. (2016) demonstrated that nasal mupirocin was associated with a 4-fold reduction in *S. aureus* bloodstream infections in this patient population.[28] However, consistent use of mupirocin can lead to mupirocin-resistant *S. aureus*.[13] A meta-analysis found that decolonization with mupirocin was associated with a 59% reduction in *S. aureus* infections among dialysis patients, but up to 10% of patients who used mupirocin become colonized with a mupirocin-resistant *S. aureus* strain.[19] Given that mupirocin prophylaxis can increase the frequency of mupirocin-resistant *S. aureus* isolates, and that the mupirocin decolonization protocol is often difficult to implement, most hemodialysis units do not routinely decolonize patients with mupirocin.[19]

Nasal PVI may be preferred over mupirocin for long-term prevention of *S. aureus* infections because it is easy to use and it has multiple targets of action—thus, the risk of PVI resistance among *S. aureus* isolates is minimal.[23,29-31] PVI has been used in healthcare for years for skin antisepsis. Recently, small, single center studies found that nasal PVI was associated with decreased surgical site infection rates, and that surgical patients preferred this product over mupirocin because it had fewer side effects and was more pleasant.[32-35] Some investigators have used PVI at hemodialysis catheter exit sites or for catheter care.[36,37] However, no published studies have evaluated nasal PVI for decolonizing patients on hemodialysis.

Our objectives are to evaluate whether decolonizing patients' noses with PVI will reduce rates of *S. aureus* BSI among patients on hemodialysis, to qualitatively evaluate the implementation of this intervention, and to assess patient and healthcare worker satisfaction with PVI. This trial will be performed at 16 outpatient hemodialysis units affiliated with five academic medical centers. These ambulatory hemodialysis units are geographically dispersed and care for both rural and urban patients who receive chronic care.

We chose the stepped-wedge CRT design for multiple reasons. First, since nasal PVI could prevent endogenous *S. aureus* infection and could prevent exogenous transmission of this organism from patient to patient, individual randomization would not allow us to adequately assess the full effect of this intervention. Second, units will serve as their own controls and as controls for other units, thus limiting selection bias and imbalance among the intervention and control units.[26] Third, the staggered starting dates can help us measure and adjust for temporal biases such as the effect of CMS policy changes that occur during the study period.

Limitations

The proposed study has three main limitations. First, nasal PVI suppresses bacteria for only 12-24 hours.[31] Thus, PVI must be reapplied before each procedure. Second, we will not compare PVI with mupirocin. Instead, our control group will be standard care, which is justified because mupirocin has not been routinely used for preventing BSI among patients on hemodialysis due to implementation barriers. Third, PVI is considered a novel intervention for patients on hemodialysis, and thus we are required to obtain informed consent from each patient. Therefore, patients who do not consent to using nasal

PVI could transmit *S. aureus* to patients who do participate in the intervention.

Significance

Nasal PVI is currently used in many hospitals to prevent surgical site infections. Our study evaluates this product in a new patient population. This large stepped-wedge cluster randomized trial aims to determine whether nasal PVI decreases rates of *S. aureus* BSI among patients on hemodialysis, and to collect data on barriers and facilitators to implementation. Given that PVI as widely available and inexpensive, is easy to use and implement, and does not cause resistance, this intervention could be more generalizable than mupirocin ointment. An effective intervention to prevent infections among patients on hemodialysis could improve outcomes among the 2 million people who receive renal replacement therapy worldwide.[38]

Trial Status

Trial is currently ongoing.

Funding Statement

This work was supported by the Agency for Health Research and Quality (AHRQ) grant number 1R01HS026724-01 and by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002537. Povidone-iodine product will be donated by 3M (funding number ISR74). AHRQ, NIH and 3M have no role in study design; collection, management, analysis, and interpretation of data; writing of the report; nor the decision to submit the report for publication.

Competing Interests: None declared.

Author Contributions: Study design: MS, RN, KD, LH, AO, LB, DD, JC, JJ, DP, SB, AV, AM, MF, DOM. Study implementation: MS, MW, RN, KD, AR, LB, JC, JJ, DP, SB, AV, AM, MF, PT, MM, EJ. Statistical analysis: RN, AO. All authors contributed to, read and approved the final manuscript. Dr. Schweizer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A; complete (please see ClinicalTrials.gov page)
Protocol version	#3	Date and version identifier	N/A; no version identifier
Funding	#4	Sources and types of financial, material, and other support	9

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Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 9
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2, 3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3, 9
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3

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Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4 (ClinicalTrials.gov)
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	3, 7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6 (study includes qualitative component to assess intervention implementation)
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A; intervention does not affect care usually received
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7

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Participant timeline	#13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrollment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A (not blinded)

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Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A (study is not blinded)
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6, 7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6, 7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised	7

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		analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	N/A (Study is IRB approved)
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4, 5

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Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A (no ancillary studies included)
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A (no provisions provided; please see attached consent form)
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A (no intended use of professional writers)
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form attached
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or	5, 6, 7, 8

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molecular analysis in the current trial and for future use in ancillary studies, if applicable

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