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Study Title: The Effect of Pre-Operative Bacterial Decolonization on Post-Operative Infection Rate for Lower Extremity Wound Healing by Second Intention

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The effect of pre-operative bacterial decolonization on post-operative infection rate for lower extremity wounds healing by second intention: A prospective study

Principal Investigator	Dr. Naomi Lawrence, Cooper University Hospital, Dermatology
Study Sponsor	Cooper University Hospital
Funding Source	None
Study Summary	In this study, we plan to expand on recent literature and assess the benefit of decolonization prior to surgical removal via Mohs surgery or surgical excision on lower extremity lesions healing by second intention.
Protocol Version	Version dated 09.12.2024

A. Research Design

A.1. Purpose/Specific Aims

The purpose of this research is to determine if pre-operative decolonization with chlorhexidine and mupirocin will significantly decrease the infection rate of wounds healing by second intention on the lower extremities.

A.1.1. Hypotheses / Research Question(s)

We hypothesize that the pre-operative mupirocin decolonization of the nares and chlorhexidine wash of the skin folds and lower extremities will significantly decrease the post-operative infection rate for lower extremity surgical wounds healing by second intention.

Background and Significance

Previous studies have demonstrated increased risk of surgical site infection on lower extremity wounds and those healing by second intention, with the most common pathogen being Staphylococcus aureus. To date, no prospective, randomized trials, investigated the utility and efficacy of surgical site infection (SSI) prophylaxis with decolonization for patients with lower extremity wounds healing by second intention. The results of this study could significantly decrease surgical site infection rates, therefore decreasing patient morbidity and healthcare costs.

In our previous study, "Incidence of Surgical Site Infections in Second Intention Healing After Dermatologic Surgery," Schimmel et al. compared a retrospective study of 5,679 patients investigating the rate of surgical site infection and associated pathogenic organisms of second intention wounds compared with sutured wounds after skin cancer extirpation. The infection rate for sutured and second intention wounds was 3.2% and 6.8%, respectively. Second intention wounds were associated with a significantly higher risk of infection compared with sutured wounds (odds ratio = 2.22, 95% confidence interval 1.63-2.99). The lower extremity (LE) had the highest overall infection rate (10.5%). Staphylococcus aureus was the most common organism cultured in both second intention (35%) and sutured wounds (81%). Pseudomonas was the second most common organism cultured in second intention wounds.

“Risk Factors for Surgical Site Infections in Dermatological Surgery” by Liu et al was an observational cohort study of 1,977 procedures in 1,407 patients investigating the parameters that lead to increased

risk of surgical site infections. Infection rates were increased in surgeries performed on the ear, larger wounds and defects closed with flaps or healed by second intention. Second intention was associated with a significantly higher risk of surgical site infection (OR 3.01, 95%CI 1.11–8.13). The surgical site infection rate of wounds healing by second intention was 6.1%. This number was higher than the accepted range in previous studies (0.7–4.2).

"Prospective study of wound infections in dermatologic surgery in the absence of prophylactic antibiotics," by Dixon et al was a 3-year prospective study investigating the incidence of infection after surgical treatment of predominantly nonmelanoma skin cancer. No patients in the study received prophylactic antibiotics. Analysis of regions of the body demonstrated that surgery below the knee (n=448) had an infection incidence of 6.92% (31/448) ($p<.0001$). A sub-analysis demonstrated that all regions below the knee were at high infection risk. No other body site demonstrated an infection incidence beyond 5% of statistical significance.

"Observations Regarding Infection Risk in Lower-Extremity Wound Healing by Second Intention," by Molina et al,was a retrospective study of 555 patients treated with MMS on the lower extremities with wounds left for second intention healing was conducted investigating the rate of infection and pathogenic organisms. Of 555 patients, 24 patients (4.3%) returned to clinic with culture-positive wound infections within 90 days of surgery. The majority (n= 15, 63%) of infections were caused by Staphylococcus aureus.

"Oral Antibiotics Versus Topical Decolonization to Prevent Surgical Site Infection After Mohs Micrographic Surgery—a Randomized, Controlled Trial," by Cherian et al was a randomized, controlled trial with 693 patients. Nasal carriers of S. aureus were randomized to receive topical decolonization with intranasal mupirocin twice daily plus 4% chlorhexidine gluconate body wash daily for 5 consecutive days before surgery or pre- and postoperative doses of oral cephalexin. Nine percent of patients receiving oral antibiotic prophylaxis and none of the patients receiving topical decolonization developed early SSI ($p = .003$).

"Randomized Controlled Trial of Preoperative Topical Decolonization to Reduce Surgical Site Infection for Staphylococcus aureus Nasal Swab-Negative Mohs Micrographic Surgery Patients," by Smith et al was a randomized controlled trial of S. aureus nasal swab-negative patients. Five days before Mohs surgery topical decolonization with nasal mupirocin and chlorhexidine body wash was started. The control group had no intervention. Results demonstrated the infection rate in the intervention group was 2% and that of the control group was 4%.

A.2. Study Design

This study is a prospective, randomized trial. Patients will be randomly placed into one of two arms. The experimental group will receive decolonization with mupirocin 2% ointment to the nares and chlorhexidine washes to the skin folds and lower extremities. The control group will not receive any pre-operative decolonization. This is not a pilot study.

A.3. Intervention

Patients in our experimental group will apply mupirocin 2% ointment to each nostril twice daily five days prior to surgery. Chlorhexidine will be applied to the skin folds and lower extremities during the five

consecutive showers prior to surgery. Patients will be instructed to let the chlorhexidine sit for one minute prior to rinsing.

A.4. Allocation to Interventional Group

Patients will be randomized to either the control (standard of care) group or the experimental (decolonization) group. A log will be kept allowing for randomization of patients into control arms. The log will alternate between study and control group. The patient will be entered into the log in the order that their telehealth was completed, which will determine their study group.

A.5. Sample Size Calculation

Our previous study determined a surgical site infection rate of ~10% in lower extremity surgical wounds healing by second intention. Given our assumption that the intervention would reduce the incidence to 5%, the minimal sample size necessary to detect a 5% absolute difference between the intervention and control group would be 424 per group for a total of 848 subjects. We plan to enroll subjects at 10 study centers in order to be able to reach the sample size required for adequate power.

A.6. Data Analysis Plan

Fisher's exact test will be used to compare categorical variables.

B. Subject Population

B.1. Description of Subject Population

This study will target any patients undergoing Mohs micrographic surgery or surgical excision on the lower extremities that will heal by second intention as determined by the surgeon performing the procedure.

B.2. Inclusion Criteria

- Individuals undergoing surgical treatment for skin cancer on the lower extremities.
- Postoperative wounds healing by second intention
- Must be at least 18 years old.

B.3. Exclusion Criteria

- Any individual taking antibiotics during the peri-operative period or post-operative period (for a reason other than surgical site infection)
- Patients with known intolerance or hypersensitivity to mupirocin or chlorhexidine.
- Patients that are currently pregnant or attempting to become pregnant.
- Patients with a history of Staphylococcus aureus infections.
- Patients with a history of heart valve or joint replacement requiring pre-operative antibiotics.

B.4. Eligibility Screening

All patients referred to our clinic for Mohs micrographic surgery or surgical excision will be screened for inclusion in this study. The scheduling staff will alert study physicians of any patient who is being scheduled for surgery on the lower extremity. Once flagged, a study physician will review the location and deem if patient an appropriate candidate for the study.

B.5. Recruitment

The dermatologic surgery staff will be educated on the inclusion criteria for this study. Patients referred to our office with lower extremity lesions will be flagged by the dermatologic surgery staff.

Once flagged, the patient's information will be sent to study personnel who will verify that the patient meets eligibility criteria. A physician will then contact the patient for a pre-operative telephone consultation to discuss participation in the study.

B.6. Informed Consent

At the pre-operative consultation, the study will be described to the subjects by the physician enrolling them. Subjects will be assured that their participation is voluntary and their level of care will not change based on their decision. They will have time to review the consent form and be able to ask any questions prior to signing the consent form.

If the pre-operative consultation is conducted virtually, the investigators will verbally explain the study and provide subjects with a copy of the consent materials electronically (via REDcap or other means) or by mail. Prior to enrollment, attempts will be made to obtain an electronic (if acceptable per institutional policies) or hand-written signature from subjects. However, if the subject is willing to participate but obtaining the signature is logistically burdensome, verbal consent will be accepted and the subject enrolled. A waiver of written documentation of consent [21 CFR §56.109(c)(1) and 45 CFR §46.117(c)(2)] will be requested of the reviewing IRB in order to enroll the subject on the study. The consent form will be reviewed during the pre-operative visit to discuss the research and ensure that the subject is fully informed. Subjects that are mailed a copy of the consent form will be asked to sign and bring it with them on the day of their surgery. Patients that sign the REDcap consent form will be asked to sign a hard copy on the day of their surgery.

C. Study Procedures

C.1. Summary of Methods and Procedures

Patients meeting eligibility criteria will be approached at their pre-operative consultation and asked to participate. After providing informed consent, as previously described, subjects will be randomly placed into one of the two arms.

Once enrolled, subjects in the experimental group will be prescribed mupirocin 2% ointment and chlorhexidine wash. Instructions for decolonization will be provided to the subjects in a "pre-procedure handout and a medication log in order to help them perform and track the decolonization protocol sufficiently. Subjects in the experimental group will follow decolonization procedures for 5 days prior to surgery.

On the day of their procedure, all subjects will be asked to fill out a demographic survey to evaluate their risk of developing infection. The demographic survey sheet will record the patients' age, sex, prior Staphylococcus aureus infections, medications, BMI over 25, smoking status, number of showers per week, and medical history of diabetes, immunosuppression, peripheral vascular disease, and nutritional deficiency. Patients' answers will be recorded in a protected, unidentified database.

Following surgery, all subjects will be asked to send in a picture of their surgical site during the postoperative period at weeks 2 and 4. Patients will submit photos of their surgical site via the Cooper RedCap system. They will receive an email prompting them to upload their photos at these points. Photographs will be evaluated by a study physician upon receipt. After that one month, the patient will be informed that they no longer need to send in any more photos.

Any patient who develops symptoms of an infection or has concerning findings on the pictures will be instructed to schedule a follow up appointment for evaluation. At this visit, their wound will be swabbed for the causative pathogens. The results from the wound culture will be shared with the patients and, if positive for pathogenic bacterial growth, will be started on antibiotics for treatment of their surgical site infection.

Subjects that do not require a follow up appointment will be followed up with a call at one month post-surgery. We will ask these patients if they developed a wound infection or if they had any issues with their surgical site.

C.2. Study Visits

On the day of the procedure, the patient will be given an envelope containing a hard copy of their official consent form to sign (if they did not bring their copy from home) and a demographic survey sheet.

All patients enrolled in the study, regardless of group, , will send in a picture of their surgical site 2 weeks and 4 weeks after their surgery. Any patient who develops symptoms of an infection or has concerning findings on the pictures they send in will be instructed to schedule a follow up appointment for evaluation. Here, their wound will be swabbed for the causative pathogens.

Any subject who develops an infection will be identified by the pictures sent to the physician or the patients' concern for infection. During this visit, a wound culture will be collected to determine the responsible pathogen. Wound culture results will be recorded within the data collection sheet.

All patients that do not develop an infection will be followed up with a call at one month. We will ask these patients if they developed a wound infection or if they had any issues with their surgical site.

C.3. Study Duration

Subjects will be asked to participate in this study for 1 month after their surgery. The overall study should take a little over a month for the treatment group since they will also have to pretreat the surgical site.

C.4. Drugs, Biologics, and Devices

All drugs used on this study are FDA approved and will be used according to label. The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use for the drugs, nor is it intended to support a significant change in the labeling for the drugs.

Mupirocin 2% ointment: Indicated for the eradication of nasal colonization with methicillin-resistant Staphylococcus aureus (MRSA) in adult and pediatric patients (aged 12 years and older) and healthcare workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of MRSA infection during institutional outbreaks of infections with this microorganism.

Clorhexidine wash: Indicated for use as an antimicrobial skin cleanser helps reduce bacteria that potentially can cause disease; for skin wound and general skin cleansing; surgical hand scrub; personnel hand wash; and preoperative skin preparation.

C.5. Safety Evaluation (if applicable)

In the case that an infection develops at the surgical site, a bacterial culture will be taken to identify the causative pathogen. This will allow the physician to properly treat the infection with appropriate antibiotics.

C.6. How Participation Differs from Standard-of-Care

It is not standard of care for patients undergoing Mohs micrographic surgery or excision on the lower extremities to decolonize with mupirocin 2% ointment and chlorhexidine. Although not standard of care, is commonly utilized by dermatologic surgeons for patients with a history of Staphylococcus aureus infections.

It is not standard of care for patients to complete a demographic surgery prior to their procedure.

C.7. Subject Withdrawal

Subjects can withdraw from the study at any time with no penalty by contacting the study team. Data that has already been collected will be retained, but not further data will be collected for research purposes.

If any patient experiences side effects to mupirocin ointment or chlorhexidine, such as burning, itching, or dryness at the application site, they will be instructed to alert the study staff. A physician from the study staff will then have a telephone consult with the patient about the side effects they are experiencing, and based on the physician evaluation, will either be asked to discontinue the medication and be removed from the study, or be counseled that it is safe to resume the study. Any patient that experiences side effects will be counseled that they may withdraw from the study at any time.

D. Additional Human Subject Considerations

D.1. Vulnerable Populations

There are no vulnerable populations involved in this study.

D.2. Economic Impact on Subjects

The only cost patients may have is the cost for the chlorhexidine and mupirocin ointment, depending on their insurance coverage.

D.3. Compensation

Patients will not be compensated for participating in this research study.

D.4. Treatment for Research-Related Injuries

The physicians that perform the procedures will provide treatment for any research-related injuries, such as infection treatment.

D.5. Sharing Study Results

If a wound culture is obtained from a patient, the results from the culture will be shared with them.

D.6. Risks

The patients involved in this study may encounter the following risks:

1. Patients have the possibility of developing side effects to the chlorhexidine and mupirocin treatment, such as burning, stinging, or dryness in the treatment area.
2. Patients may feel uncomfortable answering questions on the demographic questionnaire.
3. There is a risk of confidentiality if medical information or identity are obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

D.6.1. Minimizing Risks

The following is being done to minimize the above risks from occurring:

1. Patients can decline to answer any of the questions on the questionnaire or withdraw from the study at any point.
2. All patients will receive treatment if they develop skin infections.
3. All measures will be taken to avoid breach of PHI. All personal health information will be de-identified from the study data. All data will be stored on a password-protected computer that will not leave the Cooper Center for Dermatologic Surgery. Only study personnel will have access to the computer.
4. All patients will be provided with a telephone number that will allow them to reach a physician in our practice should they have any questions or develop symptoms concerning for infection. They will be scheduled for an appointment if the evaluating physician is concerned for possible infection. Additionally, all patients enrolled will be contacted directly by study personnel one month after the procedure to evaluate if they had or are currently having any complications at the surgical site.
5. Subjects will be screened to avoid enrollment of a patient who may be sensitive to mupirocin or chlorhexidine.
6. Subjects will be provided instructions on how to properly apply mupirocin and chlorhexidine to reduce skin irritation

D.6.2. Privacy Protections

The patient is under no obligation to discuss their involvement with anyone at the office outside of study personnel. They can schedule appointments without mentioning they are involved in a research study.

D.7. Benefits

There are no direct benefits to patients who are involved in this study. This data has the potential to change the standard of care for patients receiving dermatologic surgeries on the lower extremities healing by second intention. Currently, decolonization is not a standard of care before procedures. By showing this process reduces the rate of post-operative infections, physicians could implement this into their practice, leading to reduced morbidity, improved patient outcomes, and reduced healthcare cost burden from surgical site infections.

E. Safety Monitoring

Data and Safety Monitoring Plan

All participating sites will be required to submit reports of their adverse events on a quarterly basis. The reports will be reviewed by the Principal investigator, Dr. Ashely Decker. All participating institutions will adhere to the safety and data monitoring plans of their individual institutions in addition to submitting to Cooper on a quarterly basis.

E.1. Recording of Adverse Events (AEs).

All Adverse Events will be captured on the appropriate case report form (CRF) and reviewed by the Principal Investigator. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

AEs with start dates occurring any time after informed consent is obtained until the conclusion of study participation will be recorded. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

E.2. Relationship of AE to Study.

The relationship of each adverse event to the study procedures should be characterized based on 1) relatedness, 2) expectedness, and 3) severity.

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained study clinician based on temporal relationship and their clinical judgment. The Principal Investigator will make a final determination regarding the 1) relatedness, 2) expectedness, and 3) severity of the Adverse Event.

The relatedness of the AE will be assessed as follows:

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology.

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

Serious Adverse Events are defined by Cooper SOPs as follows: A Serious Adverse Event is any adverse event that meets any of the following conditions: 1) is life-threatening, 2) requires inpatient hospitalization or prolongation of existing hospitalization, 3) results in persistent or permanent damage (e.g. disability), 4) results in congenital anomaly/birth defect, 5) death.

E.3. Reporting of AEs and Unanticipated Problems. Any adverse events and unanticipated problems should be reported to the principal investigator by calling the 24/7 on call line. This number will be provided to them on the consent form and the post-surgical visit handout.

Follow-up Report:
All patients who report an adverse event will be evaluated by a study physician via a telehealth consultation. For any adverse events that are unexpected, a follow up report will be created and submitted to the IRB.

Auditing and Inspecting.

Participation as an investigator in this study includes acceptance of potential inspection by government regulatory authorities and applicable Cooper Health System compliance and quality assurance offices.

F. Data Management

F.1. Data Collection
Paper forms will be used to collect demographic survey. Coded data will be manually entered into a study Excel sheet stored on a shared drive.

F.2. Confidentiality
Each site has the original copies of data and their PHI, and they only enter de-identified information into a Cooper shared drive. This keeps any PHI from being shared amongst sites.

F.3. Secondary Use of Data
Patient information will not be shared with any investigators or personnel outside the principal investigator and her co-investigators. De-identified information can be shared amongst study personnel.

F.4. Records Retention
Any records of study involvement will be retained for 6 years from the date of its creation or the date when it last was in effect, whichever is later.

G. Project Management

G.1. Personnel Qualifications
The principal investigator, Dr. Naomi Lawrence, and co-investigator, Dr. Tara Jennings, are fellowship trained dermatologic surgeons. They have received the required training to perform these procedures and identify surgical site infections.

Study Finances

None

G.2. Conflicts of Interest

There are no known conflicts of interest within this study. All participating investigators must abide by institutional conflict reporting and management and are required to report any conflicts to the Principal Investigator.

H. References

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I. Appendix

Screening	Patient will be identified as a potential research subject. Their chart will be flagged for their pre-operative visit..
Pre-operative visit	During their standard pre-operative visit, the physician will inform the patient of the study. If the patient agrees to participate, a link to REDCap or a physical copy of the consent form will be sent to them. Patients will be placed into one of two arms. They will be given instructions on the pre-operative decolonization if they are placed in the experimental group.

Day of procedure	Patient will come in for their procedure. They will fill out the demographic survey and receive a hard copy of their consent form.
Post-operative management	Patients will send a picture of their surgical wound to the physician 2 weeks after and 4 weeks after their procedure. If the patient does not develop any infection, they will be called 1 month after their procedure to check on their progress.
Infection develops	Patients will be asked to report to the office. A swab will be taken of the infection site to test for the causative pathogen. Appropriate treatment will be given when the results are received.