Study Protocol with Statistical Analysis Plan

Study Title: Skin and Soft Tissue Infection (SSTI) study

NCT#: 02600871

Document Date: 03/10/2016 (IRB approval date)

Skin and Soft Tissue Infection (SSTI) study

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Background

A local Practice-Based Research Network recently reported that one in five patients presenting to clinic for a methicillin-resistant *Staphylococcus aureus* (MRSA) skin infection experienced treatment failure within 90 days, at a mean cost of $1,933 per patient. [1] In a subgroup of patients with moderate-complicated skin abscesses, failure rates were 36%, despite receipt of guideline endorsed therapy. Several clinicians reported that household contacts (HCs) of these patients later came to clinic too, with similar skin infections. Other studies have demonstrated a 28% treatment failure rate after the incision and drainage of uncomplicated cutaneous abscesses. [2] [3] These findings demonstrate a clear need for interventions to promote healing and improve outcomes in patients with skin abscesses and reduce infections in their HCs. We believe Provodine can help satisfy this critical need.

Study Design

We propose an open-label, randomized, pragmatic clinical trial for a pilot study to determine if Provodine can be used as an antiseptic and hand wash applied once daily to promote healing and improve outcomes in patients with skin abscesses and to reduce infections in their HCs. Patients will be randomized to Provodine or washing with soap and water. We have strategically selected our highest enrolling clinics from prior studies to start this investigation. If the results of this pilot study are promising, we will work with Microdermis to design and implement a follow-on statistically powered, clinical outcome study that will involve geographically distributed clinics and alternate sites around the US.

Patients

Study inclusion criteria

1. Age 18 years or older
2. Skin abscess (i.e., pus)
3. Treatment requiring incision and drainage

Study exclusion criteria:

1. Unable or unwilling to provide informed consent
2. Homeless, incarcerated, or living in a group home
3. Abscess on the face or breast
4. Abscess requiring surgical drainage in the operating room or requiring admission to the hospital
5. Intravenous drug users
6. Previous enrollment in this study
7. Documented history of iodine sensitivity

Hypothesis

We believe patients who use Provodine as an antiseptic and hand wash once daily for at least 7 days will have better healing, better health outcomes, fewer treatment failures and fewer infections themselves and among their household contacts (HCs) than those who do not use Provodine.

Specific Aims

1. Compare clinical cure rates in patients with cutaneous abscesses at 7 days
2. Compare rate of new lesion development within 30 days
3. Compare infection rates in HCs within 30 days

Methods

Patients who meet criteria for the study will be enrolled by a convenience sample and randomized to a treatment group. Each patient will have a demographic data sheet completed by one of the study investigators or research associates. The data sheet will include contact information, age, gender, ethnicity, location of the abscess, measured length and width of palpable fluctuance and induration, measured length and width of surrounding cellulitis, presence or absence of fever, and previous medical history (including history of prior skin abscesses.) Assignment to a treatment group will be by blocked randomization.

All enrolled patients will be provided with an informed consent document and an overview of the study. Baseline measurements including size of abscess (measured by ruler of palpable fluctuance and induration) and maximal diameter of the largest area of cellulitis will be recorded. Providers will outline the area of palpable fluctuance with an Aspen skin marker and delineate the surrounding area of cellulitis with a dotted line to establish baseline surface area of wound. All patients will have standard care including incision and drainage and wound culture of the abscess cavity. All patients will receive local anesthesia and additional pain management will be left to the discretion of the treating provider. Providers will make a linear incision over the length of palpable fluctuance and induration. The provider will explore the wound cavity and break apart any loculations to allow for adequate drainage of purulent discharge. The provider will obtain wound cultures and irrigate with normal saline until clear irrigation fluid drains from cavity. Swabs will be sub-cultured on blood agar plates and grown overnight for bacterial identification and antibiotic susceptibility testing.

Patients randomized to Provodine will have the abscess cavity and surrounding skin gently painted with Provodine solution. The contents of one foil packet of Provodine will be applied with

a Q-tip to the walls and floor of the abscess cavity. The contents of a second foil packet will be applied to the surrounding skin within 5 cm around the incision.

The abscess cavity of both groups will be gently packed with ¼ inch plain gauze strips and the wound will be covered with 4x4 gauze and secured with tape. Patients will be instructed to leave the wound packing in place and change the outer dressing once a day until they return at 48-72 hours for their first wound recheck.

Several studies have shown that there is no clinical benefit to antibiotics in the routine management of uncomplicated abscesses.[2,3] Patients with uncomplicated abscesses (defined as palpable abscess < 5 cm in a healthy patient with no history of diabetes, HIV, IVDA or immunocompromised state who has no systemic signs of infection) will not be treated with antibiotics. Patients who do not meet these criteria will be treated with antibiotics at the discretion of the provider.

A study investigator will evaluate the patient in the emergency department or clinic within 48- 72 hours for the initial follow up visit and the packing will be removed. Patients randomized to Provodine will have the contents of the foil packet reapplied to the walls of the abscess cavity and surrounding skin. Data that will be collected on initial recheck include presence or absence of fever, purulent drainage, erythema, and pain, as well as presence of new skin lesions. A new lesion is defined as a new abscess, pustule, carbuncle, or furuncle at least 5 cm away from the initial wound. Lesions within 5 cm of initial wound will be considered failures of the initial abscess treatment.

Study investigators will also record compliance with intervention and side effects. Compliance will be assessed by measuring the amount of opened foil packets and by patient report. The cure rate, as measured by the absence of fever, pain, erythema and purulent discharge, will be recorded as well as the overall assessment by the provider if wound is improving, unchanged, or clinically worsened.

Wound management will be left up to the discretion of the treating provider, but further incision and drainage, wound repacking and antibiotic use will be reserved for patients determined to be not clinically improving or getting worse and will be considered a treatment failure. Outcomes including clinical cure, rate of new lesion development in patients and HCs, and therapeutic changes to clinical management will be recorded.

After the packing is removed, all patients will be instructed to cleanse the abscess at home by soaking in water once a day and gently patting the wound dry. Patients will follow specific instructions for wound management once a day after washing.

After cleansing and drying the abscess, the patients randomized to the Provodine arm will wash their hands with soap and water, pat dry, and apply the contents of one foil packet of Provodine to dorsum and palmar aspects of hands and fingers and rub hands and fingers together for one minute to ensure all skin distal to the wrist is covered. They will then apply the contents of a second foil packet to the walls and floor of the abscess cavity using a Q tip applicator. The patient will then apply a third foil packet of Provodine to the skin surrounding the abscess within 5 cm diameter of the wound using a separate Q tip. After applying Provodine to the abscess and surrounding skin, they will be then gently rinse their hands with water, pat hands dry, and cover the wound with a 4x4 gauze dressing.

The patient will also be instructed to keep a Ziploc bag of empty Provodine foil packets to assess compliance at follow up visits.

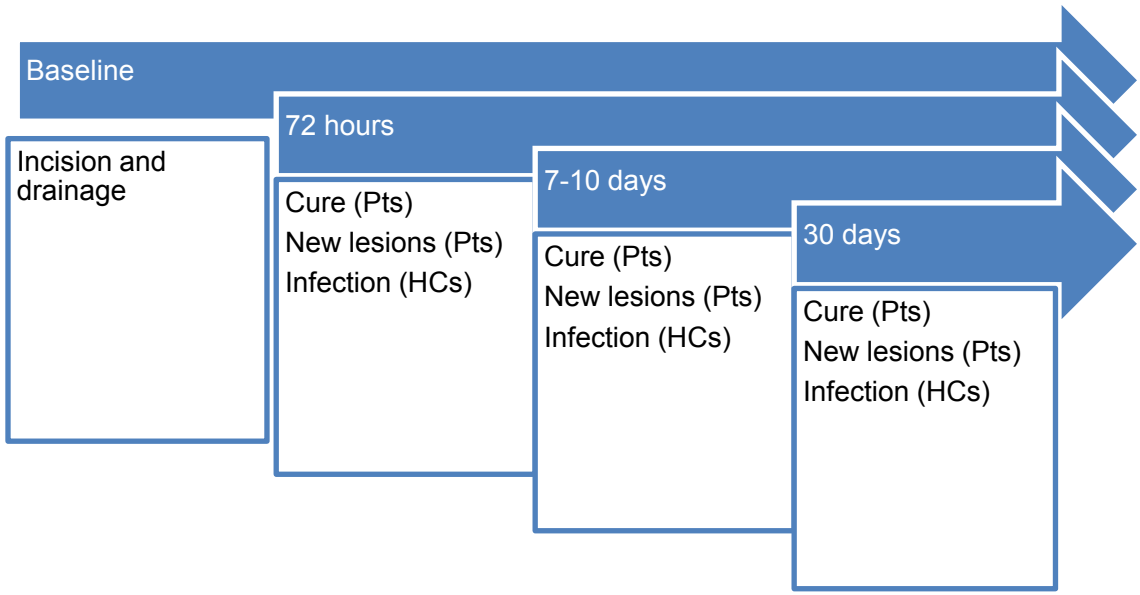
Patients randomized to standard care will cover wound with 4x4 gauze dressing and wash hands with soap and water for one minute. Patients will be instructed to continue to perform once daily cleansing/treatments until they are seen for their second wound recheck or until wound cavity has closed.

The patient will return for a 2nd visit between 7 and 10 days for a second wound recheck. Data that will be collected will be the same as on initial recheck including the presence or absence of fever, purulent drainage, erythema, and pain, as well as presence of new skin abscesses in the patient or HCs.

Study investigators will also record compliance with intervention and side effects. Compliance will be assessed by measuring the amount of opened foil packets and by patient report. The cure rate, as measured by the absence of fever, pain, erythema and purulent discharge, will be recorded. Wound management will again be left up to the discretion of the treating provider, but further incision and drainage, wound repacking and antibiotic use will be encouraged only for patients determined to be not clinically improving or getting worse and will again be considered a treatment failure. Outcomes including clinical cure, reinfection, rate of new lesion development, and therapeutic changes to clinical management will be recorded.

Patients will be called at home at 30 days to assess for treatment failures requiring additional intervention and new lesion development in patients and their HCs.

The figure below depicts the timing of assessments for patients (Pts) and household contacts (HCs). Outcomes include rate of clinical cure rate of initial abscess and rate of new lesion development. Therapeutic changes (e.g., addition of new antibiotics or additional incision and drainage), or unplanned health care encounters for the skin infection (e.g., urgent care visits, emergent care visits, or hospital admissions) will be considered treatment failures. Fisher's exact test will be used to compare outcomes between groups.



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Timeline and Estimated Costs

We will continue enrollment until 100 patients complete their second wound care follow up and estimate this will take approximately 1 year. We anticipate enrollment of about 130 patients. Microdermis will provide Provodine at no cost to the patients.

Statistical Methods

Continuously distributed outcomes will be summarized with the sample size, mean, standard deviation, median, minimum and maximum, and categorical outcomes will be summarized with frequencies and percentages. The number screened, the number of screen failures by reason, and the number randomized, and the number lost to follow-up by reason and the number completing the study by treatment group will be tabulated. Treatment groups will be contrasted with regard to cure (yes, no), new lesions (yes, no), and infections (yes, no) with Fisher's Exact tests. Adverse events, if any, will be listed by treatment group and case number and indicators of seriousness (serious, not serious), severity (mild, moderate, severe), and relation to the treatment (related to the treatment, unknown but not related to the treatment). All statistical testing will be two-sided with a significance level of 5%. The sample size was not derived from a statistical power calculation but was motivated by the pilot nature of this study. SAS Version 9.4 for Windows or R will be used throughout.

[1] Labreche MJ, Lee GC, Attridge RT, Mortensen EM, Koeller J, Du LC, Nyren NR, Trevino LB, Trevino SB, Pena J, Mann MW, Munoz A, Marcos Y, Rocha G, Koretsky S, Esparza S, Finnie M, Dallas SD, Parchman ML, Frei CR. Treatment failure and costs in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infections: a South Texas Ambulatory Research Network (STARNet) study. J Am Board Fam Med. 2013;26(5):508-17.

[2] Schmitz GR, Bruner D, Pitotti R, Olderog C, Livengood T, Williams J, Huebner K, Lightfoot J, Ritz B, Bates C, Schmitz M, Mete M, Deye G. Randomized controlled trial of trimethoprim-sulfamethoxazole for uncomplicated skin abscesses in patients at risk for community-associated methicillin-resistant Staphylococcus aureus infection.Ann Emerg Med. 2010 Sep;56(3):283-7

[3] Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. Ann Emerg Med. 2010 May;55(5):401-7